To Be Mailed

10/520,963

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number
WO 01/85745 A1

(51) International Patent Classification[7]: C07H 3/04, 15/207, 3/06, A61K 31/70

(21) International Application Number: PCT/GB01/02098

(22) International Filing Date: 11 May 2001 (11.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0011593.1	12 May 2000 (12.05.2000)	GB
60/203,598	12 May 2000 (12.05.2000)	US
09/798,004	2 March 2001 (02.03.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/85745 A1

(54) Title: INOSITOL PHOSPHOGLYCAN DERIVATIVES AND THEIR MEDICAL USES

(57) Abstract: Compounds having a mimetic or antagonistic property of an inositol phosphoglycan, and the uses of these compounds are disclosed, together with the use, e.g. to treat a condition ameliorated by administration of an IPG second messenger or an IPG antagonist thereof. Preferred compounds of the invention are based on the substituted cyclitols, and in particular, the compounds are based on the linkage of two or more sugar residues to a cyclitol.

INOSITOL PHOSPHOGLYCAN DERIVATIVES AND THEIR MEDICAL USES

Field of the Invention

The present invention relates to compounds and their uses, and in particular to compounds which have a mimetic or antagonistic property of an inositol phosphoglycan or a free GPI precursor of an IPG, and the uses of these compounds, e.g. to treat a condition ameliorated by administration of an IPG second messenger or an IPG antagonist thereof.

Background of the Invention

Many of the actions of growth factors and hormones on cells are thought to be mediated by a family of inositol phosphoglycan (IPG) second messengers [13]. It is thought that the source of IPGs is a "free" form of glycosyl phosphatidylinositol (GPI) situated in cell membranes. IPGs are thought to be released by the action of phosphatidylinositol-specific phospholipases following binding of growth factors to receptors on the cell surface. There is evidence that IPGs mediate the action of a large number of growth factors including insulin, nerve growth factor, hepatocyte growth factor, insulin-like growth factor I (IGF-I), fibroblast growth factor, transforming growth factor β, the action of IL-2 on B-cells and T-cells, ACTH signalling of adrenocortical cells, IgE, FSH and hCG stimulation of granulosa cells, thyrotropin stimulation of thyroid cells, cell proliferation in the early developing ear and rat mammary gland.

Partially characterised inositolphosphoglycans (IPGs) have been postulated to mediate the action of a number of growth factors and hormones including insulin and insulin-like growth factor I (IGF-I) [1]. Despite their isolation from several tissues type, the precise chemical structures of these IPGs are, however, still unknown and two main structural groups have been proposed on the basis of the chemical composition [2,3] which display different biological activity and tissue distribution [4]; the family of glucosamine-*myo*-inositol containing IPGs (IPG-A) and the family of *chiro*-inositol-galactosamine containing IPGs (IPG-P).

In an attempt to establish the minimal structural requirements for biological activity, a number of compounds containing some of the basic structural motifs that have been postulated for IPG mediators have been synthesised in the art [5]. These synthetic compounds include *O*-(2-amino-2-deoxy-D-glucopyranosyl)-α(1→6)-*chiro*-inositol 1-phosphate and *O*-(2-amino-2-deoxy-D-glucopyranosyl)-α(1→6)-*myo*-inositol 1-phosphate [6].

US Patent No: 6,004,938 (Hoechst) discloses a group of synthetic inositol glycans having insulin-like action. The compounds are based on 2-6 monsaccharide units linked to an inositol moiety. The examples in the patent all employ *myo*-inositol and are composed of 5 or 6 units apart from two pseudo-trisaccharide compounds G and H. Compounds G and H are HO-PO(H)O-6Man-α(1→4)-GluN-α(1→6)-(L)inositol-1,2(cyclic) phosphate and HO-PO(H)O-6Man-α(1→4)-GluN-α(1→6)-(L)inositol, otherwise known as *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate and *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol. The properties of exemplified compounds are investigated in lipogenesis and glucose transport assays employing rat fat cells.

WO96/14075 (University of Virginia) discloses a generic family of compounds D-hexosamines linked to an inositol via a β1,4-linkage. The inositols can be *myo* or *chiro*-inositol or pinitol, while the hexosamines are glucosamine or galactosamine. However, this application describes the synthesis of just two compounds 4-*O*-(2-deoxy-2-amino-β-D-galactopyranosyl)-D-pinitol and 4-*O*-(2-deoxy-2-amino-β-D-galactopyranosyl)-D-*chiro*-inositol, or in IUPAC notation *O*-(2-amino-2-deoxy-β-D-galactopyranosyl)-(1→4)-D-pinitol and *O*-(2-amino-2-deoxy-β-D-galactopyranosyl)-(1→4)-D-chiro-inositol.

WO99/06421 (University of Virginia) describes synthetic insulin mimetic substances and includes a general formula I showing β1,4-linked disaccharides. However,

despite this the compounds synthesised in this application are exactly the same as those disclosed in the applicant's earlier application, WO96/14075.

A multi-step synthesis of a IPG-P mimetic from glucose has been previously reported in Jaramillo et al [6], which discloses a compound called C4, 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*chiro*-inositol 1-phosphate. A further synthesis of C4 is described in our co-pending International Patent Application PCT/GB99/03715 (Rademacher Group Limited). Zapata et al [16] discloses three other compounds C1-C3 which are:

C1 1-D-4-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate.

C2 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate.

C3 1-D-6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1,2 cyclic-phosphate.

It remains a significant problem in the art to produce synthetic compounds which can mimic one or more of the activities of inositol phosphoglycans or which act as antagonists of IPGs.

Summary of the Invention

Broadly, the present invention relates to IPG mimetic and antagonist compounds and to methods of producing the compounds and to their medical uses. The compounds disclosed herein are useful as synthetic mimetics of IPG-P or IPG-A second messengers and/or growth factors whose action is mediated by IPGs, as synthetic mimetics of free GPI precursors or IPGs, or as competitive antagonists of IPGs. In particular, the compounds are based on the 1,6 linkage of two or more sugar residues to a cyclitol.

Accordingly, in a first aspect, the present invention provides a compound represented by the general formula:

Y-X-cyclitol

wherein:

X represents a sugar radical;

Y represents one to three sugar radicals;

the sugar radicals and inositol are individually unsubstituted or substituted with between one and four groups independently selected from:

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(OR)-NR_1R_2;

(c) sulphur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, -$S(O)_2$R, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2$R, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl, cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar;

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or substituted alkyl or aryl;

with the proviso that the compound is not *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate and *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-

(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

In a further aspect the present invention provides a compound represented by the general formula:

Y-X-α1,6-cyclitol

wherein:

X represents a sugar radical;

Y represents one to three sugar radicals;

the sugar radicals and inositol are individually unsubstituted or substituted with between one and four groups independently selected from:

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(OR)-NR_1R_2;

(c) sulphur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, -$S(O)_2$R, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2$R, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl, cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar;

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or substituted alkyl or aryl;

with the proviso that the compound is not *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate and *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

The compounds may be provided as racemic or diasteromeric mixtures, resolved or partially resolved optical isomers, and as pharmaceutically acceptable salts, esters and derivatives as discussed in more detail below.

Examples of compounds within this embodiment of the invention are RGL1014, RGL1021, RGL1022, RGL1105 and compounds 19 and 25.

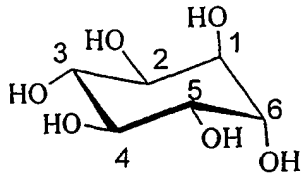
Preferably, the X or Y sugar residue is a hexose or a pentose, and may be an aldose or a ketose. The sugar residue can be a member of the D or L series and can include amino sugars, deoxy sugars and their uronic acid derivatives. Preferably, where the sugar residue is a hexose, it is selected from the group consisting of glucose, galactose or mannose, or substituted hexose sugar residues such as an amino sugar residue such as hexosamine, galactosamine or glucosamine, and more preferably D-glucosamine (2-amino-2-deoxy-D-glucose) or D-galactosamine (2-amino-2-deoxy-D-galactose). Preferred pentose sugar residues include arabinose, fucose and ribose. The X or Y sugar residue is optionally substituted at one, two, three or four positions, other than the anomeric position or the position of linkage of the other radical or to the cyclitol.

The cyclitol moiety is preferably selected from *myo*-inositol, *chiro*-inositol or pinitol (3-*O*-methyl-*chiro*-inositol), in either their D or L forms, and is optionally substituted at one or more of the positions other than the position of linkage to the sugar radical, or in the case of pinitol additionally the 3-position. The sugar radical is optionally substituted at one, two, three or four positions other than at the position of linkage to

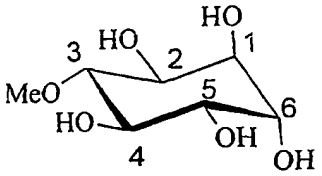
the inositol moiety (the anomeric position). Where the cyclitol moiety is substituted at the 3-position (e.g. is a pinitol or a related compound), preferably the substituent is C_{1-10} alkyl, and may be a substituted or unsubstituted primary, secondary or tertiary alkyl group. Examples of substituted groups include CF_3, $X(CH_2)_n$-O- (where X is hydrogen, or substituted or unsubstituted alkyl), CHF_2O-. A preferred alkyl group is methyl when the cyclitol is D or L-pinitol (3-*O*-methyl-*chiro*-inositol), and is optionally substituted at one or more of the positions other than the 3-position or the position of linkage to the sugar residue. In further embodiments, the cyclitol may have one or more of the hydroxyl groups through which the substituents described above are removed so that any substituent(s) are linked to the ring carbon atom. The sugar residue is optionally substituted at one, two, three, or four positions other than at the position of linkage to the inositol moiety.

Preferably the X and Y sugar residues are linked to each other and the cyclitol via a 1,1 linkage, 1,2 linkage, 1,3 linkage, 1, 4 linkage or 1,6 linkage. The linkage between the units may be an α or β linkage. The linkage of the X sugar residue to the cyclitol is generally a 1,6 linkage via one of the oxygen atoms of the cyclitol moiety. However, this oxygen atom can be replaced one or more times by $-CH_2-$ or -S- groups.

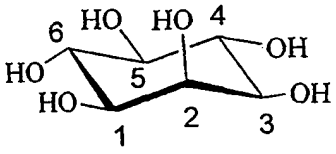
To avoid confusion, the numbering system used herein is clarified with reference to the following structures. Importantly, as the *chiro*-inositol molecule contains a C2 plane of symmetry and positions 1 and 6 are equivalents. Therefore, for instance, compounds containing a **β(1,6)** linkage can be regarded as **β(1,1)** if there are no other substituents to define priority in the numbering system. Monosaccharide residues and oligosaccharides are named and numbered according to the recommendation proposed by the Joint Commission on Biochemical Nomenclature, International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology.



chiro-Inositol



Pinitol: 3-*O*-Methyl-*chiro*-inositol



myo-Inositol

In preferred embodiments, the present invention provides a compound, or a substituted form thereof as defined above, selected from the group consisting of:

RGL1014 *O*-(D-galactopyranosyl)-α(1,4)-*O*-(2'-amino-2'-deoxy-D-glucanopyranosyl)-α(1,6)-*myo*-inositol.

RGL1021 *O*-(D-galactopyranosyl)-α(1,4)-*O*-(2'-amino-2'-deoxy-D-glucanopyranosyl)-α(1,6)-*chiro*-inositol.

RGL1022 *O*-(D-galactopyranosyl)-α(1,4)-*O*-(2'-amino-2'-deoxy-D-glucanopyranosyl)-α(1,6)-*chiro*-inositol-1-phosphate.

RGL1105 1"-D-4'-*O*-(6"-phosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)- *myo*-inositol].

Compound 25 *O*-α-D-Mannopyranosyl-(1-2)-*O*-α-D-mannopyranosyl-(1-6)-*O*-α-D-

mannopyranosyl-(1-4)-*O*-2 ammonio-2-deoxy-α-D-glucopyranosyl-(1-6)-D-*chiro*-inositol-1-phosphate.

Compound 19 *O*-β-D-galactopyranosyl-(1-4)-2-ammonio-2-deoxy-α-D-galactopyranosyl-(1-6)-D-*chiro*-inositol-1-phosphate.

In a further aspect, the present invention provides methods for making the compounds of the invention or their intermediates as set out in the following experimental description and the schemes. In a further related aspect, the present invention further relates to compounds which are the novel intermediates described herein.

In a further aspect, the present invention provides one or more of the above compounds for use in a method of medical treatment. The compounds may be useful as IPG mimetics or IPG antagonists, e.g. as competitive antagonists.

In a further aspect, the present invention provides the use of one or more of the above compounds for the preparation of a medicament for the treatment of a condition ameliorated by the administration of an inositol phosphoglycan (IPG) second messenger or an IPG antagonist. Examples of such conditions are set out in the pharmaceutical uses section below.

In a further aspect, the present invention provides a method of treating a condition in a mammal ameliorated by an inositol phosphoglycan (IPG) second messenger or an IPG antagonist, the method comprising administering to the mammal a therapeutically effective amount of one or more of the above compounds.

Embodiments of the invention will now be described by way of example and not limitation with reference to the accompanying drawings.

Brief Description of the Figures

Scheme 1 shows the synthesis of compound 4.

Scheme 2 shows the synthesis of RGL1021 from compound **4**.

Scheme 3 shows the production of RGL1022 from compound **7**.

Scheme 4 shows the production of compound **19**, a derivative of compound **4**.

Schemes 5(I) and 5(II) show the synthesis of compound **25**.

Scheme 6 shows the preparation of trisaccharide 28 (RGL 1014).

Scheme 7 shows the preparation of RGL 1105

Detailed Description

Inositol phosphoglycans (IPGs)

IPG-A mediators modulate the activity of a number of insulin-dependent enzymes such as cAMP dependent protein kinase (inhibits), adenylate cyclase (inhibits) and cAMP phospho-diesterases (stimulates). In contrast, IPG-P mediators modulate the activity of insulin-dependent enzymes such as pyruvate dehydrogenase phosphatase (stimulates) and glycogen synthase phosphatase (stimulates). The A-type mediators mimic the lipogenic activity of insulin on adipocytes, whereas the P-type mediators mimic the glycogenic activity of insulin on muscle. Both A-and P-type mediators are mitogenic when added to fibroblasts in serum free media. The ability of the mediators to stimulate fibroblast proliferation is enhanced if the cells are transfected with the EGF-receptor. A-type mediators can stimulate cell proliferation in the chick cochleovestibular ganglia.

Soluble IPG fractions having A-type and P-type activity have been obtained from a variety of animal tissues including rat tissues (liver, kidney, muscle, brain, adipose, heart) and bovine liver. IPG-A and IPG-P biological activity has also been detected in human liver and placenta, malaria parasitized RBC and mycobacteria. The ability of an anti-inositolglycan antibody to inhibit insulin action on human placental cytotrophoblasts and BC3H1 myocytes or bovine-derived IPG action on rat diaphragm

and chick cochleovestibular ganglia suggests cross-species conservation of many structural features. However, it is important to note that although the prior art includes these reports of IPG-A and IPG-P activity in some biological fractions, the purification or characterisation of the agents responsible for the activity is not disclosed.

IPG-A substances are cyclitol-containing carbohydrates, also containing Zn^{2+} ions and phosphate and having the properties of regulating lipogenic activity and inhibiting cAMP dependent protein kinase. They may also inhibit adenylate cyclase, be mitogenic when added to EGF-transfected fibroblasts in serum free medium, and stimulate lipogenesis in adipocytes.

IPG-P substances are cyclitol-containing carbohydrates, also containing Mn^{2+} and/or Zn^{2+} ions and phosphate and having the properties of regulating glycogen metabolism and activating pyruvate dehydrogenase phosphatase. They may also stimulate the activity of glycogen synthase phosphatase, be mitogenic when added to fibroblasts in serum free medium, and stimulate pyruvate dehydrogenase phosphatase.

Methods for obtaining A-type and P-type mediators are set out in Caro et al, 1997, and in WO98/11116 and WO98/11117. Protocols for determining characteristic IPG biological activities such as PDH activation, PKA inhibition, acetylCoA activation, fructose-1,6-bis-phosphatase activity and lipogenesis are well known in the art, e.g. as described in Caro et al [14].

Drug Formulation

The compounds of the invention may be derivatised in various ways. As used herein "derivatives" of the compounds includes salts, coordination complexes with metal ions such as Mn^{2+} and Zn^{2+}, esters such as *in vivo* hydrolysable esters, free acids or bases, hydrates, prodrugs or lipids, coupling partners.

Salts of the compounds of the invention are preferably physiologically well tolerated and non toxic. Many examples of salts are known to those skilled in the art. Compounds having acidic groups, such as phosphates or sulfates, can form salts with alkaline or alkaline earth metals such as Na, K, Mg and Ca, and with organic amines such as triethylamine and Tris (2-hydroxyethyl)amine. Salts can be formed between compounds with basic groups, e.g. amines, with inorganic acids such as hydrochloric acid, phosphoric acid or sulfuric acid, or organic acids such as acetic acid, citric acid, benzoic acid, fumaric acid, or tartaric acid. Compounds having both acidic and basic groups can form internal salts.

Esters can be formed between hydroxyl or carboxylic acid groups present in the compound and an appropriate carboxylic acid or alcohol reaction partner, using techniques well known in the art.

Derivatives which as prodrugs of the compounds are convertible *in vivo* or *in vitro* into one of the parent compounds. Typically, at least one of the biological activities of compound will be reduced in the prodrug form of the compound, and can be activated by conversion of the prodrug to release the compound or a metabolite of it. An example of prodrugs are glycolipid derivatives in which one or more lipid moieties are provided as substituents on the sugar residue or the cyclitol moieties, leading to the release of the free form of the compound by cleavage with a phospholipase enzyme. Examples of prodrugs include the use of protecting groups which may be removed *in situ* releasing active compound or serve to inhibit clearance of the drug *in vivo*. Protecting groups are well known in the art and are discussed further below. An example of a suitable protecting group that might be used as a prodrug is the azido group used in the synthesis below, e.g. on the 2-position of the sugar moiety.

Other derivatives include coupling partners of the compounds in which the compounds is linked to a coupling partner, e.g. by being chemically coupled to the

compound or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody or an inhibitor. Coupling partners can be covalently linked to compounds of the invention via an appropriate functional group on the compound such as a hydroxyl group, a carboxyl group or an amino group. Other derivatives include formulating the compounds with liposomes.

Pharmaceutical Compositions

The compounds described herein or their derivatives can be formulated in pharmaceutical compositions, and administered to patients in a variety of forms, in particular to treat conditions which are ameliorated by the administration of inositol phosphoglycan second messengers or IPG antagonists such as competitive antagonist.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may include a solid carrier such as gelatin or an adjuvant or an inert diluent. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. Such compositions and preparations generally contain at least 0.1wt% of the compound.

Parental administration includes administration by the following routes: intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraocular, transepithelial, intraperitoneal and topical (including dermal, ocular, rectal, nasal, inhalation and aerosol), and rectal systemic routes. For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, solutions of the compounds or a derivative thereof, e.g. in physiological saline, a dispersion prepared with glycerol, liquid

polyethylene glycol or oils.

In addition to one or more of the compounds, optionally in combination with other active ingredient, the compositions can comprise one or more of a pharmaceutically acceptable excipient, carrier, buffer, stabiliser, isotonicizing agent, preservative or anti-oxidant or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material may depend on the route of administration, e.g. orally or parentally.

Liquid pharmaceutical compositions are typically formulated to have a pH between about 3.0 and 9.0, more preferably between about 4.5 and 8.5 and still more preferably between about 5.0 and 8.0. The pH of a composition can be maintained by the use of a buffer such as acetate, citrate, phosphate, succinate, Tris or histidine, typically employed in the range from about 1 mM to 50 mM. The pH of compositions can otherwise be adjusted by using physiologically acceptable acids or bases.

Preservatives are generally included in pharmaceutical compositions to retard microbial growth, extending the shelf life of the compositions and allowing multiple use packaging. Examples of preservatives include phenol, meta-cresol, benzyl alcohol, para-hydroxybenzoic acid and its esters, methyl paraben, propyl paraben, benzalconium chloride and benzethonium chloride. Preservatives are typically employed in the range of about 0.1 to 1.0 % (w/v).

Preferably, the pharmaceutically compositions are given to an individual in a "prophylactically effective amount" or a "therapeutically effective amount" (as the case may be, although prophylaxis may be considered therapy), this being sufficient to show benefit to the individual. Typically, this will be to cause a therapeutically useful activity providing benefit to the individual. The actual amount of the compounds administered, and rate and time-course of administration, will depend on the nature

and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage etc, is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980. By way of example, and the compositions are preferably administered to patients in dosages of between about 0.01 and 100mg of active compound per kg of body weight, and more preferably between about 0.5 and 10mg/kg of body weight .

The composition may further comprise one or more other pharmaceutically active agents, either further compounds of the invention, inositol phosphoglycans, growth factors such as insulin, NGF or other growth factors listed below, or other drugs, e.g. those in use for the treatment of diabetes or other conditions set out below.

Medical Uses

As set out above, IPGs are second messengers for a range of different growth factors and hormones, including insulin, nerve growth factor, hepatocyte growth factor, endothelial growth factor, insulin-like growth factor I (IGF-I), fibroblast growth factor, transforming growth factor β, the action of IL-2 on B-cells and T-cells, ACTH signalling of adrenocortical cells, IgE, FSH and hCG stimulation of granulosa cells, thyrotropin stimulation of thyroid cells, cell proliferation in the early developing ear and rat mammary gland. Consequently, IPGs or their antagonists can be used in the treatment or amelioration of disorders mediated by the growth factors or to mimic specific growth factor or hormone biological activities.

Examples of conditions which can be treated using IPGs or IPG antagonists include, diabetes, obesity, dyslipidaemia, pre-eclampsia, neurotrophic disorders, hepatic damage and adrenal atrophy.

WO98/10791 discloses that pre-eclampsia is characterised by elevated levels of IPG-P and that it can be treated using an IPG-P antagonist. Compounds of the invention which are IPG-P antagonists, e.g. antagonists which compete with wild-type IPG-P but lack one or more of its activities, could be used in the treatment of pre-eclampsia.

The use of both IPG-P and IPG-A and IPG-A antagonists in the diagnosis and treatment of diabetes is disclosed in WO98/11435. This application discloses that in some forms of diabetes the ratio of P:A-type IPGs is imbalanced and can be corrected by administering a medicament containing an appropriate ratio of IPG-P, IPG-A or antagonist(s) thereof. In particular, it describes the treatment of obese type II diabetes (NIDDM) patients with a P-type IPG and/or an A-type IPG antagonist and the treatment of IDDM or lean type II diabetes (body mass index < 27) with a mixture of P- and A-type IPGs, typically in a P:A ratio of about 6:1 for males and 4:1 for females. The compounds and compositions of the present invention can be employed in such types of treatment. More particularly, the compounds are likely to be of use in the treatment of various form of diabetes and diabetic complications including diabetes due to insulin resistance, insulin resistance in type I diabetes and brittle diabetes, obese or lean type II diabetes, and of conditions associated with insulin resistance or insulin underproduction, such as neurotrophic disorders or polycystic ovary syndrome, lipodystrophy, age-related memory loss, and post-ischaemic damage secondary to stroke or post-transplant complications.

The compounds of this invention are also likely to be of use in controlling neuron proliferation or neurite outgrowth, either *in vitro* or *in vivo*, e.g. acting as a nerve or neurite growth factor mimetic second messenger. They may thus have applications in the treatment and/or diagnosis of any condition related to neuron proliferation or neurite differentiation. WO99/38516 discloses that IPG-A and synthetic mimetics thereof cause neuron proliferation, mimicking the action of the growth factor IGF-I. In contrast, IPG-P and synthetic mimetics thereof such as compound C4 cause neurite outgrowth. The neurons may be central (brain and spinal cord) neurons, peripheral

(sympathetic, parasympathetic, sensory and enteric) neurons, e.g. the compounds used in the regeneration of peripheral nerves, or motor neurons. Treatments may involve the treatment of damage to nerve, spinal cord or central nervous system damage secondary to trauma, or autoimmune or metabolic damage, or post-ischaemic damage secondary to stroke or post-transplant complications, motor neuron disease, neurodegenerative disorders or neuropathy. Damage to the nervous system includes the results of trauma, stroke, surgery, infection (e.g. by viral agents), ischemia, metabolic disease, toxic agents, or a combination of these or similar causes. Motor neuron disease includes conditions involving spinal muscular atrophy, paralysis or amyotrophic lateral sclerosis. Neurodegenerative disorders include Parkinson's disease, Alzheimer's disease, epilepsy, multiple sclerosis, Huntingdon's chorea and Meniere's disease.

The compounds of the invention may also be useful as hepatocyte growth factor mimetic second messengers, e.g. in the preparation of medicaments for the treatment of hepatic damage caused by infection, alcohol abuse, drug sensitivity, or autoimmunity. The compounds may also be useful as fibroblast growth factor mimetic second messengers or epidermal growth factor mimetic second messengers, e.g. in the preparation of medicaments for the promotion of wound healing following surgery or trauma or tissue damage induced by ischaemia or autoimmunity.

In other embodiments, the compounds of the invention may be useful as adrenal cell growth factor mimetic second messengers or ACTH mimetic second messengers in the preparation of a medicament for the treatment of disease states involving adrenal atrophy.

The compounds of the invention can readily be tested using the assays identified herein to determine their suitability for some or all of the medical uses described above. Thus, even compounds with a relatively low activity in one of the enzymes assays disclosed herein, may be useful by virtue of possessing a different activity, and

moreover the pattern of activities can be used to rapidly screen the compounds for suitability in the various medical applications disclosed herein.

Activity	Diabetes I	Diabetes II	Obesity	Alzheimer's	Neurotrophics
PDH Kinase	Inhibit	Inhibit	No Effect	Inhibit	No effect
PDH Phosphatase	Activate	Activate	No effect	No effect	No effect
Acetyl CoA carboxylase I *	Activate	No effect	No effect	No effect	No effect

* found in liver and adipose cytosol.

Methods of Making the Compounds

Based on the disclosure herein, the knowledge in the art and in references [5-11], the skilled person could couple sugar residues and cyclitols together, optionally with one or more substituents. An example of a further compound of the invention made by analogous syntheses is RGL1105.

Useful guidance on the synthesis of the exemplified compounds and for introducing the substituents set out herein is provided by the papers by Gigg & Gigg, Khiar & Martin-Lomas [5] and Baeschlin et al [18] and the references cited therein.

Phosphoryl groups such as phosphate, cyclic phosphate or substituted phosphate or cyclic phosphate can be substituted into the compounds of the invention by the phosphate or phosphoramidite method, Bannwath et al, *Helvetica Chemica Acta*, 70:175-186, 1987 and Yu & Fraser-Reid, *Tetrahedron Lett.*, 29:979-982, 1988.

Phosphate protecting groups can also be synthesized according to the methods

disclosed in Hoeben-Weyl, Methods of Organic Chemistry, volume 12/1 or 12/2, Teilheimer, Synthetic Methods of Organic Chemistry, Vol 45. Protecting groups for the OH of sugars include menthoxycarbonyl (MntCO), acetal (in particular, two R groups may together represent a bridging acetal such as *O*-cyclohexylidene, *O*-isopropylidene or *O*-benzylidene), *tert*-butyldimethylsilyl (TBDMS), benzyl (Bn), *tert*-butyldiphenylsilyl (TBDPS). Many protecting groups suitable for use in the syntheses and reactions of saccharides are known and are well documented in standard reference works. The choice depends in part on the route by which the compound is synthesised and/or on the uses to which it is to be put, including the reactions which it is subsequently intended to undergo.

Bioactivity Assays

The compounds of the invention can be tested for one or more the characteristic IPG-P and/or IPG-A activities mentioned above to determine whether they will be suitable for use a IPG mimetics or antagonists. Preferred assays measure the effect of the compounds on PDH phosphatase, PKA or lipogenesis. Protocols for these assays are provided in Caro et al [14]. The compounds can also be tested to determine whether they activate or inhibit other enzymes involved in insulin signalling mechanism, such as glucose-6-phosphatase.

Examples

General Methods.

All reactions were carried out under an atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and acetonitrile were distilled from calcium hydride. TLC was performed on Silica gel GF_{254} (Merck) with detection by charring with phosphomolibdic acid/EtOH. For flash chromatography, Silica Gel (Merck 230-400 mesh) was used. Columns were eluted with positive air pressure. Chromatographic eluents are given as volume to volume ratios (v/v). Routine NMR spectra were recorded with Bruker Avance DPX300 (^1H, 300 MHz), Bruker Avance

DRX400 (^{1}H, 400 MHz), and Bruker Avance DRX500 (^{1}H, 500 MHz) spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Spectra were referenced to the residual proton or carbon signals of the solvent. High-resolution mass spectra were recorded on a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. Elemental analyses were performed using a Leco CHNS-932 apparatus. The organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*.

The synthesis of D-*chiro*-inositol containing IPG-like compounds bearing complex oligosaccharide structures was envisaged using the trichloroacetimidate derivative **1** as glycosyl donor.

Glycosylation of **1** with **2** afforded pseudodisaccharides **3** in 40% yield (Scheme 1). Selective reductive opening of the benzylidene acetals in **3** with $NaBH_3CN$-HCl afforded the partially protected derivative **4** in good yield. Thus, compound **4** was used as starting material for the synthesis of some trisaccharidic IPG-like structures as indicated in Schemes 2, 3 and 4. Condensation of **4** with glycosyl donor **5** in ether afforded compound **6** in excellent yield (Scheme 2). Removal of the tert-butyldimethylsilyl group in **6** gave compound **7** in quantitative yield. After deallylation compound **7** was converted into **8** and this into the final pseudotrisaccharide **9** by catalytic hydrogenation.

Benzylation of the pseudotrisaccharide intermediate **7** yielded **10** (Scheme 3) that was deallylated to give **11**. Phosphorylation of **11** using the phosphoramidite procedure gave **12** that was then hydrogenated to be converted into the final pseudotrisaccharide **13** in good yield.

The synthetic approach giving rise to the corresponding IPG-like structure with a β configuration of the terminal D-galactopyranosyl unit is shown in Scheme 4. Treatment of glycosyl acceptor **4** with trichloroacetimidate **14** gave rise to the fully

protected pseudotrisaccharide **15** in good yield. Zemplen deacetylation of **15** followed by conventional benzylation yielded **16** that was deallylated to give **17**. Phosphorylation of **17** gave **18** which was transformed into **19** after catalytic hydrogenation.

The synthesis of pseudopentasaccharide **25** was carried out following the strategy indicated in Schemes 5(I) and 5(II). Condensation of the trisaccharide trichloroacetimidate **20** with acceptor **44** afforded the pseudopentasaccharide derivative **21** in reasonable yield. Removal of the pivaloyl group in **21** followed by conventional benzylation yielded compound **22** in quantitative yield. Deallylation of **22** (Scheme 5(II)) gave **23** phosphorylation of which yielded **24**. Final catalytic hydrogenation of **24** gave rise to the pseudopentasaccharide **25**.

1-*O*-(2-Azido-2-deoxy-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl)-6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (3)

A mixture **1** (520 mg, 0.985 mmol) and **2** (382 mg, 0.657 mmol) was dissolved in anhydrous CH_2Cl_2 (6.6 mL) and treated with a solution (2.50 μL) of trimethylsilyl triflate (80 μL) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1.5 h and then 100 μL of the above solution of TMSOTf was added. After an additional hour with stirring (174 mg, 0.328 mmol) in CH_2Cl_2 (1.5 mL) was added and stirring was continued for 2h. The mixture was the treated with Et_3N, evaporated to dryness and the residue fractionated on column chromatography (Hexane 8: AcoEt 1) to yield **3** (130.5 mg, 49%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.21 (m, 30H, ArH), 5.79 (ddt, J_1= 5.6 Hz, J_2= 10.5 Hz, J_3= 17.1 Hz, 1H, OCH_2CH=CH_2), 5.51 (s, 1H, CH benzyliden), 5.17 (dd, J_1= 1.5 Hz, J_2= 17.2 Hz, 1H, OCH_2CH=C*H*H), 5.13 (dd, J_1= 1.5 Hz, J_2= 10.4 Hz, 1H, OCH_2CH=CH*H*), 4.97-4.76 (m, 10H, AB System), 4.70 (d, J= 3.8 Hz, 1H, $H_{1'}$), 4.25-4.17 (m, 2H, $H_{5'}$ + O*CH*HCH=CH_2), 3.99 (t, J_1= 9.4 Hz, 1H, $H_{3'}$), 3.97 (m, 1H, O-CH-*H*-CH= CH_2), 3.95 (m, 1H, $H_{6'eq}$), 3.97-3.74 (m, 6H, ChiroIns), 3.64 (t, J_1= 9.3 Hz, 1H, $H_{4'}$), 3.56 (t, J= 10.3 Hz, 1H, $H_{6'ax}$), 3.49 (dd, J_1= 3.7 Hz, J_2= 9.8 Hz, 1H, $H_{2'}$).

1-*O*-(2-Azido-2-deoxy-3,6-di-*O*-benzyl-α-D-glucopyranosyl)-6-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (4)

To a solution of **3** (716 mg, 0.757 mmol) in THF (19 mL) 4Å molecular sieves were added and the mixture stirred for 30 min. Then a 1M solution of sodium cyanoborohydride in THF (15 mL, 15.14 mmol) and a 1M solution of HCl in ether was added until the evolution of gas ceased. The mixture was then treated with saturated aqueous solution of $NaHCO_3$ and the organic layer washed with saturated NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexane 4: AcoEt 1) to give **4** (575 mg, 80%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.23 (m, 30H, Ar-H), 5.82 (ddt, J_1= 5.6 Hz, J_2= 10.4 Hz, J_3= 17.2 Hz, 1H, OCH_2CH=CH_2), 5.21 (broad dd, J_1= 1.6 Hz, J_2= 17.2 Hz, 1H, OCH_2CH=CHH), 5.16 (broad dd, J_1= 1.6 Hz, J_2= 10.4 Hz, 1H, OCH_2CH=CHH), 4.96-4.65 (m, 10H, AB System), 4.74 (d, J= 3.6 Hz, 1H, $H_{1'}$), 4.44 (d, J= 12.0 Hz, 1H, AB System), 4.32 (d, J= 12.1 Hz, 1H, AB System), 4.22 (broad, dd, J_1= 5.4 Hz, J_2= 13.0 Hz, 1H, $OCHHCH$=CH_2), 4.12 (m, 1H, $H_{5'}$), 4.0 (m, 1H, $OCHHCH$=CH_2), 4.04-3.78 (m, 6H, ChiroIns), 3.76 (m, 2H, $H_{3'}$ + +$H_{4'}$), 3.45 (dd, J_1= 3.6 Hz, J_2= 10.0 Hz, 1H, $H_{2'}$), 3.38 (dd, J_1= 3.5 Hz, J_2=10.4 Hz, 1H, $H_{6'b}$), 3.27(dd, J_1= 4.2 Hz, J_2= 10.4 Hz, 1H, $H_{6'a}$), 2.39 (d, J= 1.6Hz, 1H, $OH_{4'}$).

O-(2,3,4-Tri-*O*-benzyl-6-*O*-*tert*-butyl diphenylsilyl-α-D-galactopyranosyl)-(1-4)-*O*-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-1-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*--inositol (6)

To a solution of **4** (144 mg, 0.152 mmol) and **5** (253 mg, 0.304 mmol) in ether (3 mL) 4Å molecular sieves was added and the mixture stirred at room temperature for 15 min. Then a solution (98 µL) of TMSOTf in ether (40µL in 2 mL) was added and the mixture stirred at room temperature. After 1h **5** (85 mg) in ether (1 mL) was added. After 1h, Et_3N was added and the mixture was filtered, evaporated to dryness and the residue was purified by column chromatography (hexane 8: AcoEt 1) to give **6** (201, 3 mg, 82%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.60-7.08 (m, 55H, ArH), 5.79 (m, 1H, OCH_2CH= CH_2), 5.50 (d, J= 3.6 Hz, H_{1c}), 5.17 (m, 1H, OCH_2CH= CHH), 5.12 (m,

1H, $OCH_2CH=CHH$), 4.97-4.48 (m, 16H, AB System), 4.75 (d, J= 3.7 Hz, H_{1b}), 4.32 (d, J= 12.1 Hz, 1H, AB System), 4.23-4.16 (m, 3H, AB System + H_{5b} + $OCHHCH=CH_2$), 4.05 (t, J= 3.7 Hz, 1H), 4.01-3.78 (m, 12H, $OCHHCH=CH_2$ + H_{4b} + H_{3b} + H_{2c} + H_{3c} + 7H), 3.73-3.64 (m, 2H), 3.52 (dd, J_1= 4.1 Hz, J_2= 10.7 Hz, 1H, H_{6b}), 3.45-3.41 (m, 2H, H_{6b} + H_{2b}), 1.06 (s, 9H, ^{t}BuSi).

_O_-(2,3,4-Tri-_O_-benzyl-α-D-galactopyranosyl)-(1-4)-_O_-(2-azido-3,6-di-_O_-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-1-_O_-allyl-2,3,4,5-tetra-_O_-benzyl-D-_chiro_--inositol (7)

To a solution of 6 (197.7 mg, 0.122 mmol), 1M solution of TBAF (0.190 mL) was added and the mixture was stirred at room temperature. After 3h, the mixture was treated with ice and extracted with CH_2Cl_2. The organic layer was dried and evaporated and the residue was purified by column chromatography (Hexane 3: AcOEt 1→ Hex 2: AcOEt 1) to give 7 (285 mg, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.11 (m, 45H, ArH), 5.78 (m, 1H, $OCH_2CH=CH_2$), 5.52 (d, J= 3.6 Hz, 1H, H_{1c}), 5.18 (m, 1H, $OCH_2CH=CHH$), 5.14 (m, 1H, $OCH_2CH=CHH$), 4.98-4.38 (m, 18H, AB System), 4.76 (d, J_1= 4.20 Hz, 1H, H_{1b}), 4.19 (m, 1H, $OCHHCH=CH_2$), 4.14 (m, 1H, H_{5b}), 4.04-3.76 (m, 12H, 6 ChiroIns + H_{4b} + H_{2c} + H_{3b} + H_{3c} + $H4_c$ + $OCHHCH=CH_2$), 3.62 (m, 2H, H_{5c} + H_{6b}), 3.52 (m, 1H, H_{6c}), 3.48 (dd, J_1= 3.6 Hz, J_2= 10.1 Hz, 1H, H_{2b}), 3.35 (m, 1H, H_{6c}), 3.29 (dd, J_1= 1.9 Hz, J_2= 11.4 Hz, 1H, H_{6b}). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.03, 139.00, 138.74, 138.69, 138.45, 138.23, 138.04, 134.85, 128.48, 128.46, 128.43, 128.38, 128.35, 128.33, 128.31, 128.29, 129.26, 127.96, 127.86, 127.77, 127.70, 127.63, 127.57, 127.55, 127.47, 127.44, 127.41, 127.27, 117.20, 97.99 (anomeric C), 97.16 (anomeric C), 81.94, 81.85, 80.49, 79.94, 78.91, 78.23, 76.13, 75.90, 75.76, 74.94, 74.65, 74.33, 74.22, 74.18, 73.81, 73.75, 73.59, 73.26, 73.00, 72.53, 71.52, 71.04, 68.39, 64.05, 62.20.

_O_-(2,3,4-Tri-_O_-benzyl-α-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-_O_-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-2,3,4,5-tetra-_O_-benzyl-D-_chiro_-inositol (8)

A solution of the iridium catalyst in anhydrous THF ($5.9\text{-}10^{-3}$ M solution, 166 μL)

previously treated under a hydrogen atmosphere for 30 minutes was added over a solution of **7** (45 mg, 0.033 mmol) in anhydrous THF (0.33 ml). The mixture was stirred at room temperature for 1.5 h and then THF (1.9 mL), NBS (8.4 mg, 0.047 mmol) and water (116 μL) were added and the mixture was stirred for 5 min, treated with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried and evaporated and the residue was purified by column chromatography (Hexane 2: AcOEt 1) to give pure **8** (41.2 mg, 44%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.11 (m, 45H, ArH), 5.54 (d, *J*= 3.6 Hz, 1H, H_{1c}), 5.01-4.38 (m, 18H, AB System), 4.85 (d, *J*= 3.8 Hz, 1H, H_{1b}), 4.16-4.14 (m, 2H, H_{5c} + H_{5b}), 4.08-3.78 (m, 10H, ChiroIns x 3 + H_{4b} + H_{2c} + H_{3b} + H_{4c} + H_{3c} + $2H_{6c}$), 3.63 (broad t, *J*= 6.3 Hz, 1H, H_{2a}), 3.56-3.47 (m, 3H, ChiroIns x 1 + H_{6b} + H_{2b}), 3.35 (m, 1H, H_{1a}), 3.21 (m, 1H, H_{6b}), 2.71 (s, 1H, OH_{1a}), 2.53 (broad s, 1H, OH_{6c}). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.91, 138.84, 138.65, 138.45, 138.24, 138.11, 138.05, 128.52, 128.46, 128.43, 128.41, 128.37, 128.36, 128.33, 128.31, 128.29, 128.28, 128.26, 128.23, 128.15, 128.00, 127.97, 127.94, 127.92, 127.86, 127.79, 127.69, 127.66, 127.62, 127.54, 127.51, 127.44, 127.40, 127.35, 127.32, 127.27, 127.25, 127.24, 127.22, 97.93 (anomeric C), 97.33 (anomeric C), 81.76, 81.29, 80.45, 80.02, 78.95, 78.33, 76.14, 75.89, 75.72, 75.56, 74.65, 74.33, 74.04, 73.92, 73.75, 73.60, 73.25, 72.98,72.91, 72.52, 72.10, 68.15, 67.32, 63.99, 62.19, 29.73, 29.56.

O-(α-D-galactopyranosyl)-(1-4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-(1-6)-D-*chiro*-inositol (9, RGL 1021)

To a solution of **8** (28 mg, 0.021 mmol) in MeOH (4.7 mL), five drops of AcOH and 10% Pd/C (100 mg) were added. The mixture was stirred at room temperature under a hydrogen atmosphere for 2.5 h and then filtered over Celite, washed with methanol and evaporated to give pure **9 (RGL 1021)** (9.3 mg, 88%). ^1H NMR (D_2, 500 MHz): δ 5.50 (broad s, 1H, H_{1c}), 5.36 (broad s, 1H, H_{1b}), 4.33-3.60 (m, 17H), 3.48 (broad d, *J*= 9.0 Hz, H_{2b}).

O-(2,3,4,6-Tetra-O-benzyl-α-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-

2-deoxy-α-D-glucopyranosyl)-(1-6)-1-*O*-allyl-2,3,4,5-tetra-*O*-benzyl-D-*chiro*-inositol (10)

Compound 7 (90.6 mg, 0.066 mmol) in DMF (1.3 mL) was treated with sodium hydride (5.25 mg, 0.131 mmol) and benzyl bromide (11.71 μL, 0.098 mmol) at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, methanol was added and the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous ammonium chloride and then saturated aqueous sodium chloride, dried over Na_2SO_4, evaporated and purified by column chromatography (Hexane 5: AcOEt 1→ Hex 2: AcOEt 1) to give pure **10** (87.5 mg, 91%) as a syrup. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.10 (m, 50 H, ArH), 5.79 (m, 1H, OCH_2CH= CH_2), 5.52 (d, J= 3.7 Hz, 1H, H_{1c}), 5.17 (m, 1H, OCH_2CH=C*H*H), 5.13 (m, 1H, OCH_2CH=CHH), 5.00-4.62 (m, 14H, AB System), 4.77 (d, J= 3.5 Hz, 1H, H_{1b}), 4.57-4.46 (m, 3H, AB System), 4.33 (d, J= 12.3 Hz, 1H, AB System), 4.24 (d, J= 11.9 Hz, 1H, AB System), 4.19 (d, J= 11.9 Hz, 1H, AB System), 4.17 (m, 2H, H_{5b} + OC*H*HCH= CH_2), 4.06 (t, J= 9.5 Hz, 1H, H_{4b}), 4.01 (m, 1H, H_{2c}), 3.95-3.87 (m, 5H, H_{3b} + H_{4c} + H_{3c} + H_{5c} + OCH*H*CH=CH_2), 4.2-3.75 (m, 6H, ChiroIns), 3.66 (dd, J= 3.1 Hz, J_2= 11.0 Hz, 1H, H_{6b}), 3.47 (m, 2H, H_{2b} + H_{6c}), 3.38 (dd, J_1= 5.5 Hz, J_2= 8.5 Hz, 1H, H_{6c}), 3.34 (dd, J_1= 1.6 Hz, J_2= 10.8 Hz, 1H, H_{6b}). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.78, 138.70, 138.61, 138.36, 138.32, 138.15, 137.97, 134.86, 128.36, 128.33, 128.32, 128.29, 128.27, 128.24, 128.22, 128.21, 128.19, 128.02, 127.95, 127.93, 127.91, 127.73, 127.71, 127.61, 127.57, 127.53, 127.48, 127.47, 127.45, 127.39, 127.33, 117.17, 98.40 (anomeric C), 96.98 (anomeric C), 81.94, 81.85, 80.48, 79.92, 78.94, 78.06, 77.31, 77.06, 76.80, 76.08, 75.83, 75.79, 74.83, 74.71, 74.55, 74.47, 74.24, 73.76, 73.70, 73.42, 73.30, 73.02, 72.87, 72.69, 72.49, 70.81, 69.88, 68.55, 64.05.

O-(2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1-6)-2,3,4,5 tetra-*O*-benzyl-D-*chiro*-inositol (11)

A solution of the iridium catalyst in anhydrous THF (5.9×10^{-3} M solution, 300 μL) previously treated under a hydrogen atmosphere for 30 minutes was added over a solution of **10** (87 mg, 0.059 mmol) in anhydrous THF (0.6 mL). The mixture was

stirred at room temperature for 1h and then THF (3.4 ml), NBS (15.3 mg, 0.086 mmol) and water (208 μL) were added and the mixture was stirred again at room temperature for 10 min, treated with a saturated solution of $NaHCO_3$. The reaction mixture was then extracted with CH_2Cl_2, washed with saturated NaCl dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexane 3: AcoEt 1) to give pure **11** (70.8 mg, 84%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.12 (m, 50H, ArH), 5.55 (d, *J*= 3.7 Hz, 1H, H_{1c}), 5.02-4.42 (m, 17H, AB System), 4.85 (d, *J*= 3.7 Hz, 1H, H_{1b}), 4.31 (d, *J*= 12.2 Hz, 1H, AB System), 4.25 (d, *J*= 11.7 Hz, 1H, AB System), 4.20 (d, *J*= 11.7 Hz, 1H, AB System), 4.19-4.15 (m, 2H, ChiroIns x 1 + H_{5b}), 4.08 (m, 1H, H_{4b}), 4.06 (m, 1H, H_{1a}), 4.03 (dd, J_1= 3.7 Hz, J_2= 10.2 Hz, H_{2c}), 3.98-3.86 (m, 7H, H_{3c} + H_{5c} + H_{3b} + H_{6b} + ChiroIns x 3), 3.80 (t, *J*= 9.2 Hz, 1H, H_{4c}), 3.60 (dd, J_1=3.2 Hz, J_2= 11.0 Hz, 1H, ChiroIns), 3.50-3.47 (m, 2H, H_{2b} + ChiroIns), 3.39 (dd, J_1= 5.5 Hz, J_2= 8.6 Hz, H_{6b}), 3.28 (dd, J_1= 1.8 Hz, J_2= 11.0 Hz, 1H, ChiroIns). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.95, 138.92, 138.75, 138.67, 138.62, 138.40, 138.35, 138.17, 138.16, 137.98, 137.52, 137.42, 137.40, 137.38, 137.36, 137.35, 137.34, 137.32, 137.31, 137.27, 137.25, 137.24, 137.22, 137.21, 137.17, 137.13, 137.11, 137.09, 137.01, 127.99, 127.95, 127.92, 127.73, 127.72, 127.63, 127.55, 127.53, 127.49, 127.48, 127.44, 127.40, 127.38, 127.37, 127.33, 98.30 (anomeric C), 97.25 (anomeric C), 81.76, 81.30, 80.44, 80.04, 78.97, 78.22, 76.09, 75.86, 75.75, 75.30, 74.84, 74.72, 74.20, 74.09, 73.70, 73.43, 73.30, 73.02, 72.78, 72.68, 70.89, 69.84, 68.48, 68.42, 67.30, 64.03.

_O_-(2,3,4,6-Tetra-_O_-benzyl-α-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-_O_-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-2,3,4,5-tetra-O-benzyl-1-_O_-(dibenzyloxyphosphoryl)-D-_chiro_-inositol (12)

To a solution of **11** (59 mg, 0.041 mmol) in a 1:1 mixture of dichloromethane-acetonitrile (1 mL), *N*, *N*-diisopropyl-dibenzyl phosphoramidite (30.5 μL, 0.091 mmol) and tetrazole (13.1 mg, 0.186 mmol) were added and the mixture was stirred for 1h at room temperature. The reaction mixture was cooled to 0 °C and *t*-butyl hydroperoxide (4.7 M isooctane solution, 90 μL) was added and stirring continued for

1h. The solution was then evaporated to dryness and the residue was purified by column chromatography (Hex 6: AcoEt 1) to give pure **12** as a syrup (67.6 mg, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.4-7.1 (m, 55H, ArH), 5.54 (d, J= 3.7 Hz, 1H, H_{1c}), 5.02-4.44 (m, 21H, AB System), 4.87 (dd, J_1= 4.8 Hz, J_2= 8.4 Hz, 1H, H_{1a}), 4.79 (d, J= 4.8 Hz, 1H, H_{1b}), 4.33 (d, J= 12.2 Hz, 1H, AB System), 4.24 (d, J= 11.7 Hz, 1H, AB System), 4.18 (d, J= 8.7 Hz, 1H, AB System), 4.13 (t, J= 3.8 Hz, 1H, H_{6b}), 4.11-4.04 (m, 3H, H_{5b} + H_{4b} + H_{2a}), 4.02 (dd, J_1= 3.3 Hz, J_2= 10.3 Hz, 1H, H_{2c}), 3.97 (m, 1H, H_{4c}), 3.91 (broad t, J= 6.8 Hz, 1H, H_{5c}), 3.87 (m, 2H, H_{3c} + H_{3b}), 3.83 (t, J_1= 9.1 Hz, 1H, H_{4a}), 3.74 (t, J= 9.5 Hz, 1H, H_{3a}), 3.71 (dd, J_1= 3.3 Hz, J_2= 9.7 Hz, 1H, H_{5a}), 3.62 (dd, J_1= 2.4 Hz, J_2= 11.2 Hz, 1H, H_{6b}), 3.49 (m, 2H, H_{2b} + H_{6c}), 3.38 (dd, J_1= 5.3 Hz, J_2= 8.6 Hz, 1H, H_{6c}), 3.28 (broad d, J= 9.5 Hz, 1H, H_{6b}). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.88, 138.74, 138.71, 138.57, 138.43, 138.30, 138.19, 138.15, 137.99, 137.95, 128.63, 128.58, 128.56, 128.53, 128.48, 128.44, 128.43, 128.40, 128.38, 128.36, 128.34, 128.30, 128.28, 128.25, 128.23, 128.22, 128.19, 128.18, 128.16, 128.12, 128.11, 128.09, 128.05, 128.02, 128.01, 128.00, 127.98, 127.93, 127.87, 127.80, 127.78, 127.73, 127.66, 127.63, 127.56, 127.52, 127.48, 127.46, 127.43, 127.41, 127.37, 127.34, 98.32 (anomeric C), 97.71 (anomeric C), 81.37, 81.02, 80.68, 79.00, 77.92, 77.88, 77.50, 77.26, 76.12, 75.90, 75.75, 74.85, 74.73, 74.71, 74.66, 74.30, 74.02, 73.89, 73.44, 73.08, 72.73, 72.70, 72.65, 72.62, 72.40, 71.17, 69.81, 69.59, 69.55, 69.33, 69.28, 69.26, 69.21, 68.46, 68.42, 64.10.

_O_-α-D-galactopyranosyl-(1-4)-2-ammonio-2-deoxy-α-D-glucopyranosyl-(1-6)-D-_*chiro*-inositol-1-phosphate (13, RGL 1022)

To a solution of **12** (62.8 mg, 0.037 mmol) in methanol (4.3 mL) 10% Pd on C (176 mg), AcOH/AcONa buffer (0.2 M, pH 5, 4.3 mL) and THF (0.6 mL) were added. The mixture was stirred under a hydrogen atmosphere for 24 h and then filtered a lyophilised to give **13**. ^{1}H NMR (D_2O, 500 MHz): δ 5.49 (broad s, 1H, H_{1c}), 5.12 (broad s, 1H, H_{1b}), 4.53 (m, 1H, H_{1a}), 4.26-3.6 (m, 17H). ^{31}P NMR (D_2O, 202 MHz): δ 3.38.

O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-1-O-allyl-2,3,4,5-tetra-O-benzyl-D-*chiro*-inositol (15)

To a solution of compound **14** (36.3 mg, 0.074 mmol) and compound **4** (38.8 mg, 0.041 mmol) in anhydrous ether (0.5 mL) powdered 4Å molecular sieves were added and the mixture was stirred for 30 min at room temperature. Then TMSOTf (0.11 M solution in ether, 33 μL) was added and the mixture was stirred at room temperature for 45 min. The mixture was treated with Et_3N, filtered and evaporated. The residue was fractionated by column chromarography (Hexane 3: AcoEt 1) to give **15** (36.8 mg, 70%). ^1H NMR ($CDCl_3$, 500 MHz): 7.43-7.21 (m, 30H, ArH), 5.81 (m, 1H, $OCH_2CH=CH_2$), 5.20 (m, 1H, $OCH_2CH=CHH$), 5.19 (m, 1H), 5.14 (m, 1H, $OCH_2CH=CHH$), 5.05 (d, J= 10.5 Hz, 1H, AB System), 5.02 (dd, J_1= 10.5 Hz, J_2= 8.1 Hz, 1H, H_{2c}), 4.96-4.89 (m, 3H, AB System), 4.79 (m, 2H, AB System), 4.73 (d, J= 3.8 Hz, 1H, H_{1b}), 4.69-4.62 (m, 6H, $H_{5c} + H_{3c} + H_{6c}$ + 3H), 4.25 (d, J= 8.2 Hz, 1H, H_{1c}), 4.21 (m, 1H, $OCHHCH= CH_2$), 4.18 (d, J= 12.2 Hz, 1H, AB System), 4.0-3.71 (m, 12H, $OCHHCH= CH_2 + H_{6b} + H_{4b} + H_{3a} + H_{5b} + H_{3b}$ + 6H), 3.47 (dd, J_1= 3.7 Hz, J_2= 10.1 Hz, 1H, H_{2b}), 3.42 (m, 2H), 3.17 (broad d, J= 10.8 Hz, 1H, H_a), 2.07 (s, 3H, CH_3COO), 1.98 (s, 3H, CH_3COO), 1.92 (s, 3H, CH_3COO), 1.69 (s, 3H, CH_3COO). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.19, 170.15, 170.02, 168.94, 139.06, 138.89, 138.75, 138.70, 138.26, 137.40, 134.87, 128.71, 128.40, 128.36, 128.32, 128.20, 128.14, 127.69, 127.63, 127.56, 127.54, 127.45, 127.24, 99.85 (anomeric C), 97.75 (anomeric C), 81.94, 81.71, 80.02, 78.88, 78.17, 77.28, 77.03, 76.77, 76.11, 76.07, 75.84, 75.70, 75.20, 73.95, 73.54, 73.42, 73.26, 72.61, 70.90, 70.54, 70.40, 69.41, 66.88, 66.74, 63.16, 60.94, 60.45, 20.67, 20.62, 20.56, 20.51,.

O-(2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-1-O-allyl-2,3,4,5-tetra-O-benzyl-D-*chiro*-inositol (16)

To a solution of **15** (32 mg, 0.025 mmol) in MeOH (0.5 mL) a 1M solution of sodium methoxide (20 μL) was added and the mixture stirred for 20 min at room temperature.

Then the mixture was evaporated to dryness, toluene was added and evaporated. The residue was solved in DMF (0.5 mL) and sodium hydride (8 mg, 0.2 mmol) and benzyl bromide (18 μL, 0.15 mmol) were added. The mixture was stirred overnight at room temperature and then cooled to 0 °C, methanol was added and the mixture was extracted with AcOEt. The extract was washed with saturated aqueous ammonium chloride, and saturated aqueous sodium chloride, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexanes: AcOEt 1) to give pure **16** (31.5 mg, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.06 (m, 50H, ArH), 5.74 (m, 1H, OCH_2CH= CH_2), 5.15 (m, 1H, OCH_2CH=C*H*H), 5.12 (d, *J*= 10.5 Hz, 1H, AB System), 5.10 (m, 1H, OCH_2CH= CH*H*), 4.96-4.59 (m, 14H, AB System), 4.71 (d, *J*= 4.1 Hz, 1H, H_{1b}), 4.49 (m, 2H, AB System), 4.31 (d, *J*= 12.3 Hz, 1H, AB System), 4.25 (d, *J*= 7.7 Hz, 1H, H_{1c}), 4.20 (m, 2H, AB System), 4.17-4.12 (m, 2H, OC*H*HCH=CH_2 + 1H), 4.04 (t, *J*= 9.0 Hz, 1H, H_a), 3.97 (dd, J_1= 3.1 Hz, J_2= 9.7 Hz, 1H, H_a), 3.93 (m, 1H, H_{4b}), 3.9 (m, 1H, OCH*H*CH= CH_2), 3.86-3.71 (m, 7H, H_{3b} + H_{2c} + 4H_a + 1H), 3.45 (t, *J*= 8.6 Hz, 1H, H_{4c}), 3.42 (dd, J_1= 3.6 Hz, J_2= 10.3 Hz, 1H, H_{2b}), 3.3-3.21 (m, 4H, H_{3c} + H_{5c} + 2H).

_O_-(2,3,4,6-Tetra-_O_-benzyl-β-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-_O_-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-2,3,4,5-tetra-_O_-benzyl-D-*chiro*-inositol (17)

A solution of the iridium catalyst in anhydrous THF (5.9 x 10^{-3} M solution, 92 μL) previously treated under a hydrogen atmosphere for 30 min was added to a solution of **16** (26.1 mg, 0.018 mmol) in anhydrous THF (0.18 mL). The mixture was stirred to room temperature for 1.5 h and cooled to 0 °C THF (1 mL), NBS (4.58 mg, 0.025 mmol) and water (60 μL) were added and the mixture was stirred at 0 °C for 20 min. Then saturated aqueous $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried and evaporated. The residue was purified by column chromatography (Hexane 3: AcOEt 1→ Hex 2: AcOEt 1) to give pure **17** (21.1 mg, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.07 (m, 50H, ArH), 5.13 (d, *J*= 10.1 Hz, 1H, AB System), 4.89-4.60 (m, 13H, AB System), 4.78 (d, *J*= 3.8 Hz, 1H, H_{1b}), 4.48 (m, 2H, AB System), 4.32 (d, *J*= 11.7 Hz,

1H, AB System), 4.24 (d, J= 7.7 Hz, 1H,H_{1c}), 4.18 (m, 2H, AB System), 4.12-4.04 (m, 5H, AB System x 2 + H_{5c} + H_{4b} + H_a), 3.99 (dd, J_1= 2.2, J_2= 9.5 Hz, 1H, H_a), 3.87-3.68 (m, 8H, H_{4c}+ H_{3b} + H_{2c} + H_{5b} + H_{1a} + H_{6c} + 2H), 3.45 (t, J= 8.6 Hz, 1H, H_a), 3.42 (dd, J_1= 3.8 Hz, J_2= 10.1 Hz, 1H, H_{2b}), 3.3-3.23 (m, 3H, H_{3c} + 2H_a), 3.12 (broad d, J= 10.2 Hz, 1H, H_{6c}), 1.83 (s, 1H, OH_{1a}). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.07, 138.74, 138.71, 138.66, 138.57, 138.49, 138.44, 138.26, 138.14, 137.99, 128.63, 128.51, 128.42, 128.37, 128.35, 128.33, 128.29, 129.19, 128.16, 127.98, 127.93, 127.83, 127.80, 127.77, 127.76, 127.74, 127.73, 127.71, 127.67, 127.64, 127.61, 127.58, 127.52, 127.50, 127.48, 127.44, 127.39, 127.37, 127.34, 127.27, 102.66 (anomeric C), 98.40(anomeric C), 82.36, 81.69, 81.36, 80.06, 79.67, 78.26, 76.78, 76.61, 76.20, 76.01, 75.71, 75.25, 75.03, 74.75, 73.76, 73.40, 73.21, 73.13, 73.02, 72.72, 72.68, 71.09, 68.12, 67.99, 67.52, 67.36, 63.28, 25.64.

_O_-(2,3,4,6-Tetra-_O_-benzyl-β-D-galactopyranosyl)-(1-4)-(2-azido-3,6-di-_O_-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-2,3,4,5-tetra-_O_-benzyl-1-_O_-(dibenzyloxyphosphoryl)-D-_chiro_-inositol (18)

To a solution **17** (21 mg, 0.015 mmol) in a 1:1 mixture of CH_2Cl_2: CH_3CN (0.4 mL), N, N-diisopropyl dibenzyl phosphoramidite (16 μL, 0.046 mmol) and tetrazole (8 mg, 0.112 mmol) was added and the mixture was stirred for 3h at room temperature. The reaction mixture was then cooled to 0°C and t-butyl hydroperoxide (4.7 M isooctane solution, 34 μL) was added and stirring was continued for 1h. The solution was then evaporated to dryness and the residue was purified by column chromatography (cyclohexane 3: AcOEt 1) to give **18** (39%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.04 (m, 60H, ArH), 5.09 (d, J= 10.1 Hz, 1H, AB System), 4.97-4.44 (m, 20H, AB System), 4.88 (d, J= 4.0 Hz, 1H, H_{1a}), 4.73 (d, J= 3.8 Hz, H_{1b}), 4.31 (d, J= 12.0 Hz, 1H, AB System), 4.27 (d, J= 7.7 Hz, 1H, H_{1c}), 4.19 (m, 2H, AB System), 4.13-4.01 (m, 4H, H_{2a} + 1H_a + 2H_b), 3.85 (m, 1H, 1H_c), 3.80-3.67 (m, 6H, H_{3b} + H_{2c} + 3H_a + 1H), 3.47-3.39 (m, 2H, H_{2b} + 1H), 3.30-3.39 (m, 2H, H_{2b} + 1H), 3.30-3.23 (m, 3H, 1H_c + 2H), 3.14 (m, 1H, 1H_b). ^{31}P NMR ($CDCl_3$, 202 MHz): δ -2.20.

O-β-D-galactopyranosyl-(1-4)-2-ammonio-2-deoxy-α-D-galactopyranosyl-(1-6)-D-*chiro*-inositol-1-phosphate (19)

To a solution of **18** (3.3 mg, 1.9 μmol) in methanol (0.22 mL) AcOH/AcONa buffer (0.2 M, pH5, 0.22 mL) and 10% Pd/C (5 mg) were added. The mixture was stirred under a hydrogen atmosphere for 2 h and then filtered and liophylized. The residue was passed through a sephadex G-10 column (10% EtOH in water) to give pure **19**. ^{1}H NMR (D_2O, 500 MHz): δ 5.13 (broad s, 1H, H_{1b}), 4.56 (m, 1H, H_{1a}), 4.50 (d, J= 7.5 Hz, 1H, H_{1c}), 4.24-3.57 (m, 17H). ^{31}P NMR (D_2O, 202 MHz): δ 3.36.

O-(3,4,6-Tri-O-benzyl-2-O-pivaloyl-α-D-mannopyranosyl)-(1-2)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1-6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-2-deoxy-α-D-glycopyranosyl)-(1-6)-1-O-allyl-2,3,4,5-tetra-O-benzyl-D-*chiro*-inositol (21)

To a mixture **20** (104 mg, 0.067 mmol), 14 (89.41 mg, 0.094 mmol) and 4Å molecular sieves in CH_2Cl_2 (2 mL) at room temperature was added TMSOTf (1.0 μL, 0.005 mmol). After 1.5 h at room temperature the reaction mixture was neutralized with Et_3N, filtered and evaporated to dryness. The residue was purified on column chromatography (cyclohexane 10: AcOEt 1) to give **21** (62.2 mg, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.41-7.06 (m, 75 H, ArH), 5.86-5.77 (m, 1H, OCH_2CH=CH_2), 5.48 (dd, J= 3.1 Hz, J_2= 2.2 Hz, 1H, H_{2e}), 5.26 (d, 1H, J= 2.0 Hz, H_{2d}), 5.21-5.12 (m, 2H, OCH_2CH=CH_2), 5.01 (d, 1H, J= 2.0 Hz, H_{1e}), 4.96-3.34 (m, 63H), 1.72 (s, 9H, ^{t}Bu).

O-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1-2)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1-6)-(2,3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1-6)-1-O-allyl-2,3,4,5-tetra-O-benzyl-D-*chiro*-inositol (22)

To a solution of **21** (97.3 mg, 0.042 mmol) in 1:1 methanol: THF (1.35 mL), sodium methoxide in methanol (1M solution, 94 μL) was added and the mixture was stirred overnight at room temperature. The solution was evaporated to dryness, toluene was

added to the residue and evaporated. The residue was solved in DMF (1.35 mL) and NaH (3.3 mg) and benzyl bromide (7.5 μL) were added. The mixture was stirred at room temperature for 24 h, cooled to 0 °C, treated with MeOH and extracted with CH_2Cl_2. The extract was washed with sat. NH_4Cl, sat. NaCl, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexane 6: AcoEt 1) to give pure **22** (99%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.09 (m, 80H, ArH), 5.82 (m, 1H, $OCH_2CH{=}CH_2$), 5.28 (d, *J*= 2.1 Hz, 1H, H_{1d}), 5.23-5.12 (m, 3H, $OCH_2CH{=}CH_2$ + $1H_d$), 4.98-4.76 (m, 9H, AB System), 4.90 (m, 1H, $1H_d$), 4.70 (d, *J*= 3.6 Hz, 1H, $1H_b$), 4.70-3.35 (m, 55H).

O-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1-2)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1-6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3,4,5-tetra-O-benzyl-D-*chiro*-inositol (23)

A solution of the iridium catalyst in anhydrous THF (5.9×10^{-3} M, solution, 88 μL) previously treated under a hydrogen atmosphere for 30 min was added over a solution of **22** (40 mg, 0.071 mmol) in THF (0.2 mL). The mixture was stirred for 45 min and THF (1 mL), NBS (4.38 mg, 0.025 mmol) and water (60 μL) were added and the mixture was stirred for 5 min, treated with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (Hexane 4: AcOEt 1→ Hexane 2: AcOEt 1) to give **23** (93%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.06 (m, 80H, ArH), 5.26 (d, *J*= 2.2 Hz, 1H, $1H_d$), 5.11 (d, *J*= 2.0 Hz, 1H, $1H_d$), 4.95 (m, 1H, AB System), 4.86 (d, *J*= 2.0 Hz, 1H, $1H_d$), 4.89-3.2 (m, 62H).

O-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)-(1-2)-(3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-(1-6)-(2,3,4-tri-O-benzyl-α-D-mannopyranosyl)-(1-4)-(2-azido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-2,3,4,5-tetra-O-benzyl-1-O-(dibenzylphosphoryl)-D-*chiro*-inositol (24)

To a solution of **23** (12.8 mg, 0.005 mmol) in a 1:1.5 mixture of CH_2Cl_2: CH_3Cl (1.6

mL), N, N-diisopropyl dibenzyl phospharamidite (22 μL, 0.067 mmol) and tetrazole (5.7 mg, 0.080 mmol) was added and the mixture stirred for 45 min at room temperature. The mixture was cooled to 0 °C and t-butyl hydroperoxide (4.7M isooctane solution, 50 μl) was added and stirring was continued for 30 min. The mixture was evaporated to dryness and the residue was purified by column chromatography (Hexane 1: Ether 2) to give **24** (60%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (m, 90H, ArH), 5.27 (d, *J*= 2.3 Hz, 1H, $1H_d$), 5.11 (d, *J*= 2.0 Hz, 1H, $1H_d$), 4.96-3.26 (m, 68H).

_O_-α-D-Mannopyranosyl-(1-2)-_O_-α-D-mannopyranosyl-(1-6)-_O_-α-D-mannopyranosyl-(1-4)-_O_-2 ammonio-2-deoxy-α-D-glucopyranosyl-(1-6)-D-*chiro*-inositol-1-phosphate (25)

A solution of **24** (3 mg) in THF-EtOH (1:11) (50 μL) containing NH_4OAc (0.5 mg) was stirred for 12h under atmospheric pressure of H_2 with 10% Pd/C, the filtered over Celite and concentrated. The crude mixture was passed through Sephadex G.25 eluting with H_2-EtOH (10:1). Liophylisation gave **25** as a white powder. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.26 (bs, 1H), 5.17 (bs, 1H), 5.06 (bs, 1H), 4.8 (bs, 1H), 4.52-3.54 (m, 29H), 2.97 (bs, 1H).

(_O_-α-D-Galactopyranosyl-(1-4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-(1-6)-_D_-*myo*-inositol) (28, RGL 1014).

To a mixture of compound 1 (114 mg, 1 equiv.), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl trichloroacetimidate (210 mg) and 4Å molecular sieves in CH_2Cl_2 (20 mL) at room temperature was added TMSOTf (1.6 μL, 0.008 mmol). After 1h, the reaction mixture was neutralised with solid $NaHCO_3$, filtered over Celite and evaporated. The crude mixture was purified by flash chromatography to give a pure fully protected trisaccharide (210 mg). To a solution of this fully protected trisaccharide (149 mg) in wet chloroform (3 mL), trifluoroacetic acid (0.4 mL) was added and the mixture was kept for 18 h at room temperature. Saturated aqueous $NaHCO_3$ was then added at O° C, the aqueous layer extracted with CH_2Cl_2 (3 x 10

mL) and the combined organic extracts were dried and concentrated. The residue was purified by column chromatography (EtOAc: hexane 1:25) to afford a colourless oil that was dissolved in EtOH (1.8 mL) containing 10% Pd/C. The reaction mixture was stirred for 18 h under atmospheric pressure of hydrogen, filtered over Celite and concentrated. The crude product was purified through a Sephadex G-25 column and liophylised to give pure **2**. ^{1}H-RMN (D_2O, 500MHz): 5.39 (1 H, d, *J*= 3.4, Gal H- 1); 5.19 (1 H, d, *J*= 3.6, GlcN H- 1); 3.98 (1 H, t, *J*= 2.75, Ins H- 2); 3.97 (1 H, ddd , *J*= 10.3, 3.4, 2.8, GlcN H- 5); 3.94 (1 H, m, Gal H- 5); 3.92 (1 H, m, Gal H- 4); 3.84 (1 H, dd, *J*= 10.6, 8.9, GlcN H- 3); 3.81 (2 H, m, GlcN H- 6); 3.79 (1 H, m, Gal H- 2); 3.77 (1 H, m, Gal H- 3); 3.7 (1 H, m, Ins H- 1); 3.67 (2 H, m, Gal H- 6); 3.66 (1 H , m, Ins H- 6); 3.62 (1 H, dd, *J*= 8.9, 10.3, GlcN H- 4); 3.61 (1 H, dd, *J*= 9.7, 10.2, Ins H- 4); 3.48 (1 H, dd, *J*= 10.2, 2.9, Ins H- 3); 3.32 (1 H, dd, *J*= 8.9, 9.7, Ins H- 5); 2.78 (1 H, dd, *J*= 3.6, 10.6, GlcN H- 2). ^{13}C-NMR (D_2O, 125.7 MHz) 100.4 (GlcN C-1), 100.2 (Gal C-1), 80.9 (Ins C-6), 77.5 (GlcN C-4), 74.5 (GlcN C-3), 73.4 (Ins C-5), 72.8 (Ins C-2), 72.8 (Ins C-4), 72.1 (Gal C-5), 71.9 (Ins C-1), 71.3 (Ins C-3), 71.1 (GlcN C-5), 69.7 (Gal C-3), 69.5 (Gal C-4), 69.0 (Gal C-2), 61.5 (Gal C-6), 60.8 (GlcN C-6), 55.4 (GlcN C-2).

Assay Data

PDH activation at 100μM

RGL1021	14%

PKA inhibition at 0.1μM

RGL1014	2%
RGL1022	47%

References:

The references mentioned herein are all expressly incorporated by reference.

[1](a) Varela-Nieto et al, *Comp. Biochem. Physiol.*,. 115B:223-241, 1996; (b) Strälfors, *Bioassays*, 19:327-335, 1997; (c) Field, *Glycobiology,* 7:161-168, 1997; d) Jones & Varela-Nieto, *Int. J. Biochem. Cell Biol.*, 30:313-326, 1998.

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WO98/11116 and WO98/11117 (Rademacher Group Limited).

WO98/11435 and WO98/10791 (Rademacher Group Limited).

WO99/38516 (Rademacher Group Limited).

Claims:

1. A compound represented by the general formula:

Y-X-cyclitol

wherein:

X represents a sugar radical;

Y represents one to three sugar radicals;

the sugar residue is unsubstituted or substituted with between one and four groups, and the cyclitol is unsubstituted or is further substituted with between one and four groups, the group or groups being indepedently selected from:

(a) phosphoryl groups such as phosphate -O-P(O)$(OH)_2$; thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); cyclic phosphate;

(b) other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2 and phosphoramidate -O-P(O)(OR)-NR_1R_2;

(c) sulphur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, -$S(O)_2$R, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulphamide -$NHSO_2NH_2$;

(d) amino groups such as -NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3^-$, -$NHSO_2$R, -N$(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as -NH-C(S)-NH_2;

(e) hydroxy groups and substituted hydroxy groups such as -OR_3, where R_3 is C_{1-10} unsubstituted or substituted alkyl, e.g. CHF_2 or CF_3, alkoxyalkyl, aryloxyalkyl, cycloalkyl, alkenyl (unsubstituted alkyl), alkylene (C_{3-7} cycloalkyl), -OCOR, aryl, heteroaryl, acetal, or where two hydroxyl groups are joined as a ketal;

(f) halogen substituents such as fluorine or chlorine;

(g) hydrogen, e.g. to provide a deoxy sugar;

wherein R, R_1 and R_2 are independently hydrogen or C_{1-10} unsubstituted or

substituted alkyl or aryl;

or a derivative thereof;

with the proviso that the compound is not *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-ammonio-2-deoxy-α-D-glucopyranosyl)-(1→6)-L-*myo*-inositol-1,2-cyclic phosphate and *O*-(6-hydrogenphosphonate-α-D-mannopyranosyl)-(1→4)-(2-amino-2-deoxy-α-D-glucopyranosyl)-L-*myo*-inositol.

2. The compound of claim 1, wherein the X sugar residue and the cyclitol are 1,6 linked.

3. The compound of claim 1 or claim 2, wherein the sugar reside and cyclitol are α linked.

4. The compounds of claim 1 or claim 2 wherein the sugar residue and cyclitol are β linked.

5. The compound of any one of the preceding claims, wherein the cyclitol is selected from *myo*-inositol, *chiro*-inositol or pinitol.

6. The compound of any one of the preceding claims, wherein the sugar residue is a hexose or a pentose, or substituted forms thereof.

7. The compound of claim 6, wherein the sugar residue is a hexose selected from the group consisting of glucose, galactose or mannose.

8. The compound of claim 6, wherein the sugar residue is a hexosamine.

9. The compound of claim 8, wherein the hexosamine is galactosamine or glucosamine.

10. The compound of any one of the preceding claims, wherein the cyclitol is a D or L-enantiomer.

11. The compound of any one of the preceding claims which is selected from the group consisting of:

RGL1014 *O*-(D-galactopyranosyl)-α(1,4)-*O*-(2'-amino-2'-deoxy-D-glucanopyranosyl)-α(1,6)-*myo*-inositol;

RGL1021 *O*-(D-galactopyranosyl)-α(1,4)-*O*-(2'-amino-2'-deoxy-D-glucanopyranosyl)-α(1,6)-*chiro*-inositol;

RGL1022 *O*-(D-galactopyranosyl)-α(1,4)-*O*-(2'-amino-2'-deoxy-D-glucanopyranosyl)-α(1,6)-*chiro*-inositol-1-phosphate;

RGL1105 1"-D-4'-*O*-(6"-phosphate-α-D-mannopyranosyl)-[1'-D-6-*O*-(2'-amino-2'-deoxy-α-D-glucopyranosyl)- *myo*-inositol];

Compound 25 *O*-α-D-Mannopyranosyl-(1,2)-*O*-α-D-mannopyranosyl-(1,6)-*O*-α-D-mannopyranosyl-(1,4)-*O*-2 ammonio-2-deoxy-α-D-glucopyranosyl-(1,6)-D-*chiro*-inositol-1-phosphate; and

Compound 19 *O*-β-D-galactopyranosyl-(1,4)-2-ammonio-2-deoxy-α-D-galactopyranosyl-(1,6)-D-*chiro*-inositol-1-phosphate;

or derivatives thereof.

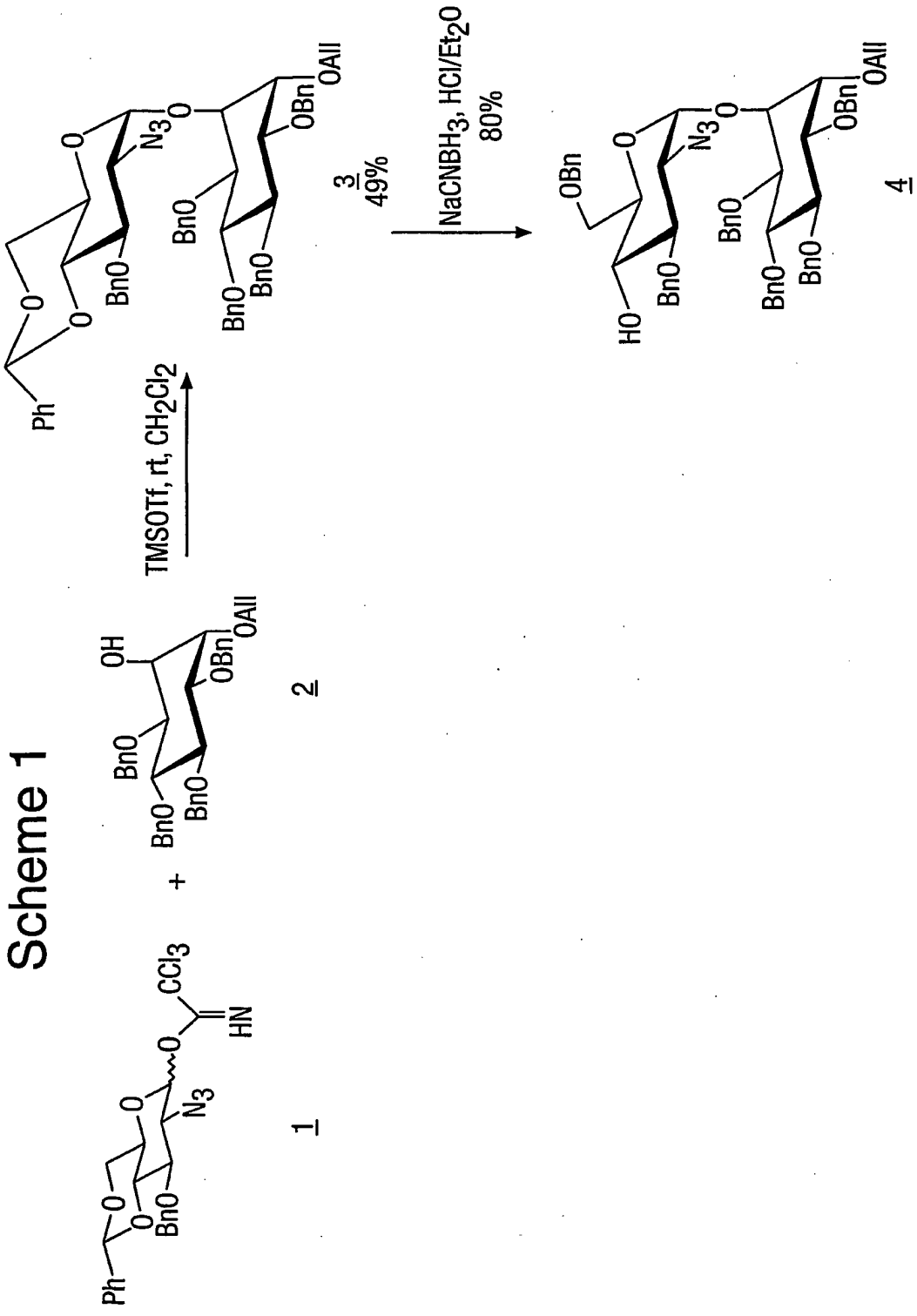
12. A composition comprising a compound of any one of the preceding claims, in combination with a pharmaceutically acceptable carrier.

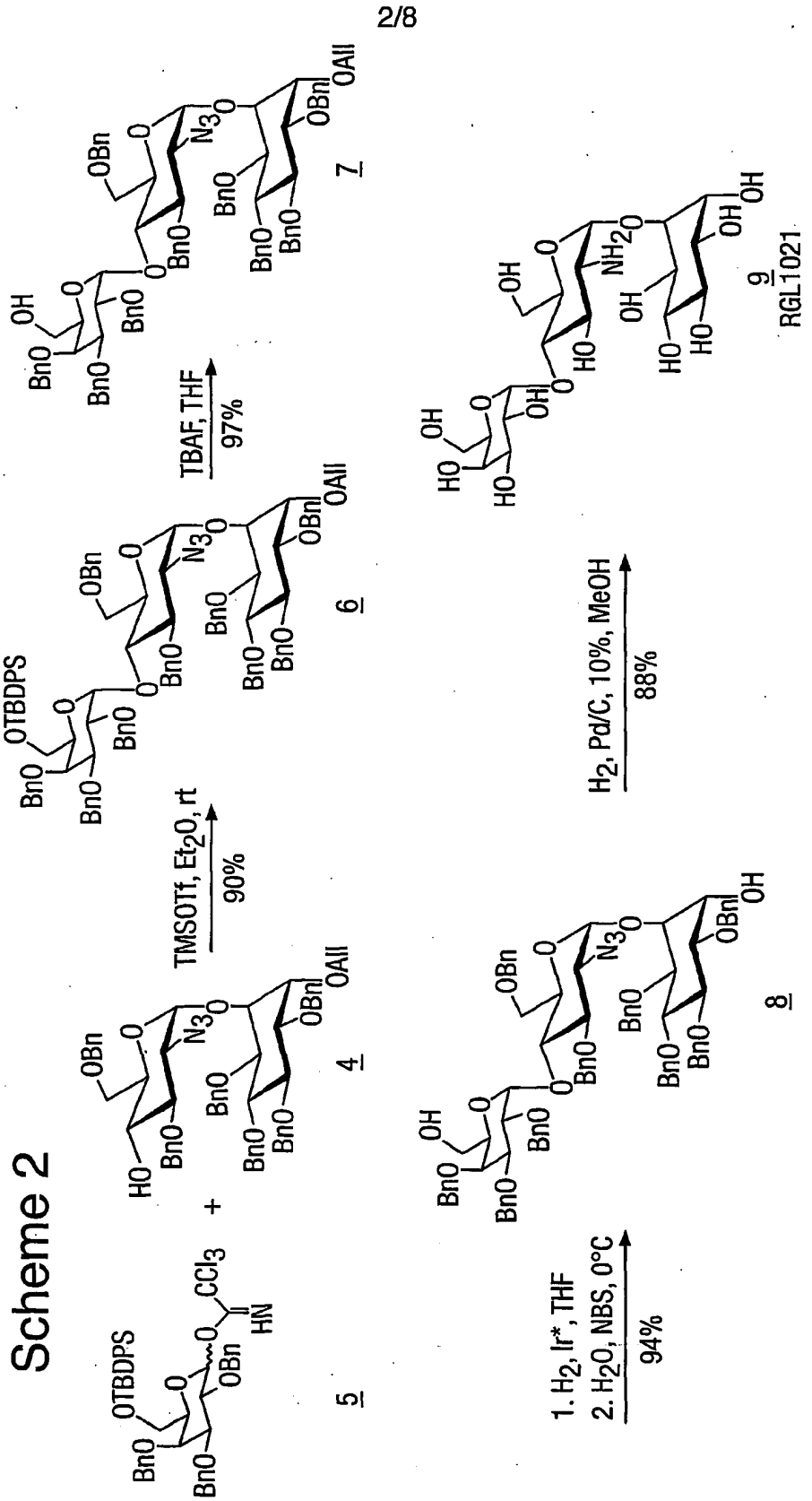
13. A method of treating a condition in a mammal ameliorated by an inositol phosphoglycan (IPG) second messenger or an IPG antagonist, the method comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1 to 11.

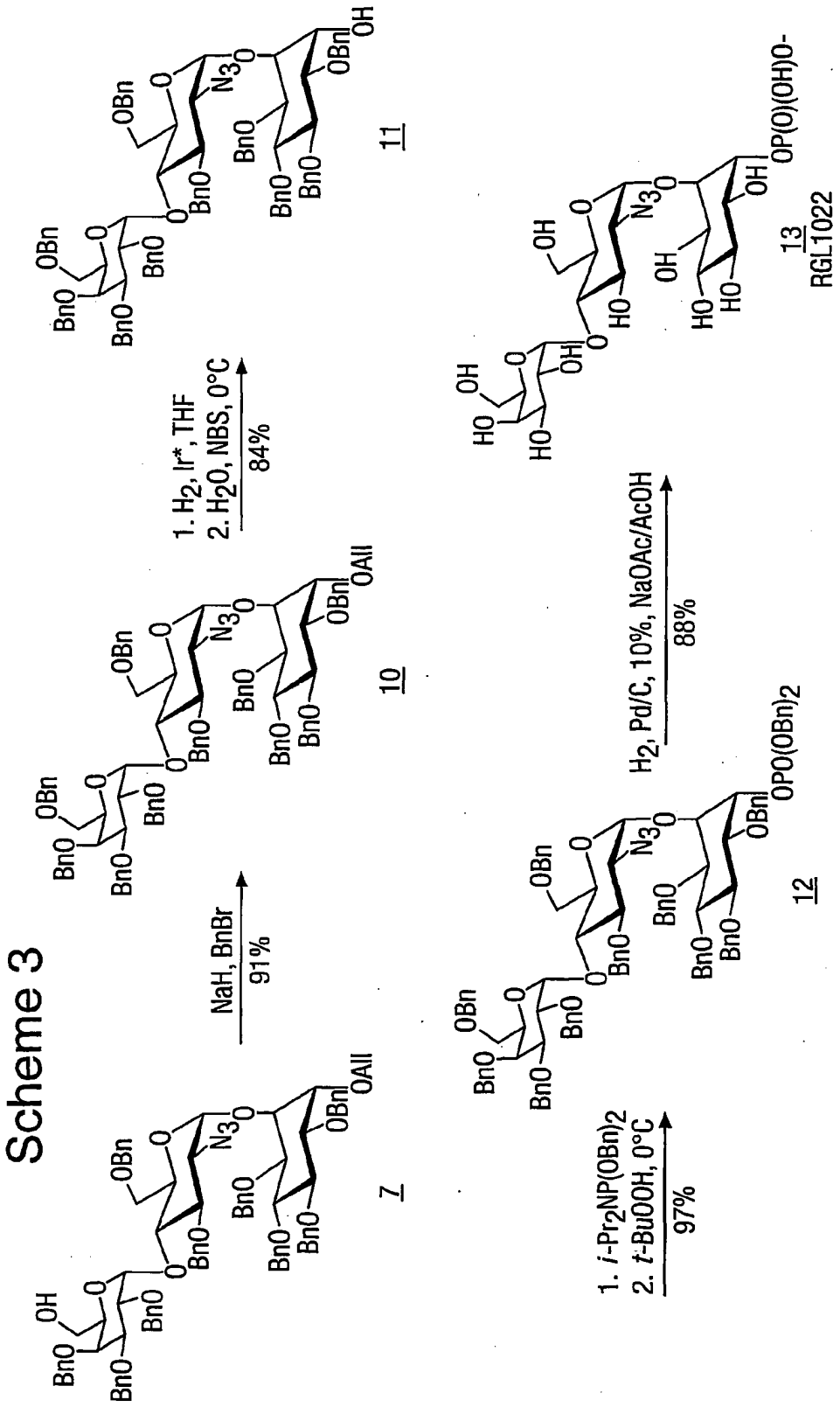
14. A compound of any one of claims 1 to 11 for use in a method of medical treatment.

15. Use of a compound of any one of claims 1 to 11 for the preparation of a medicament for the treatment of a condition ameliorated by the administration of an inositol phosphoglycan (IPG) second messenger or an IPG antagonist.

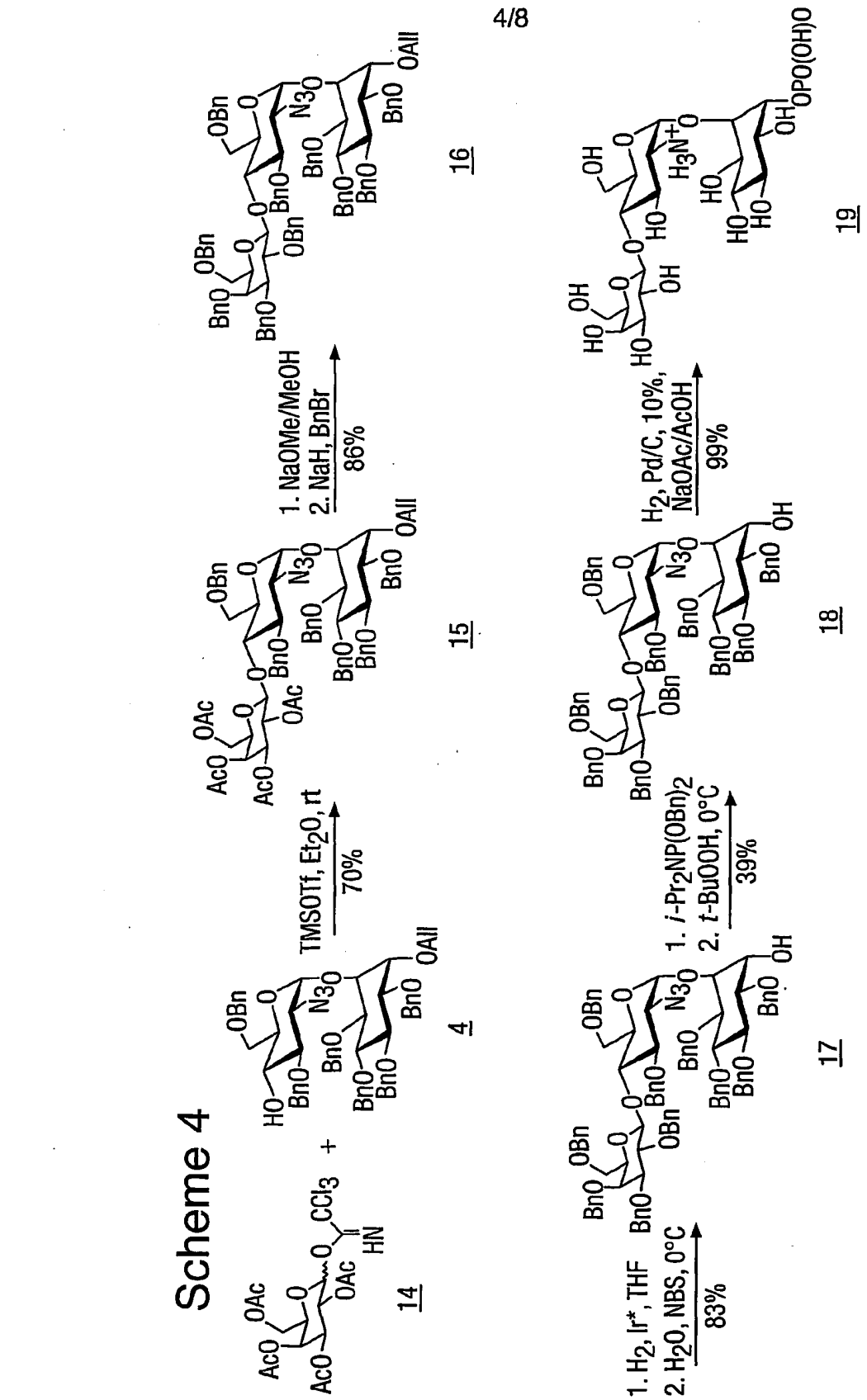
5

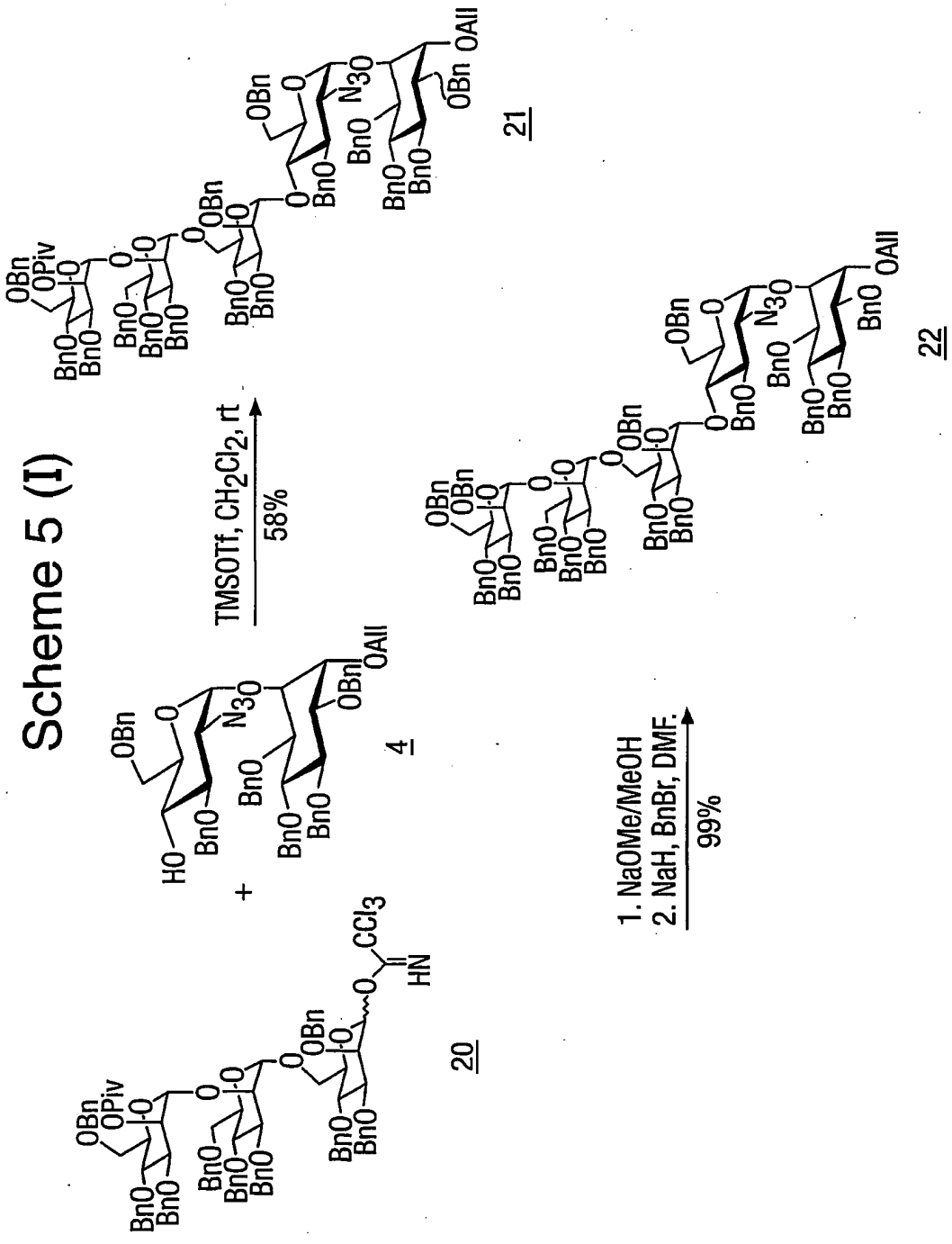

Scheme 1
1
2
3
49%
4
80%
TMSOTf, rt, CH2Cl2
NaCNBH3, HCl/Et2O


Scheme 2
5
4
TMSOTf, Et2O, rt
90%
6
TBAF, THF
97%
7
1. H2, Ir*, THF
2. H2O, NBS, 0°C
94%
8
H2, Pd/C, 10%, MeOH
88%
9
RGL1021

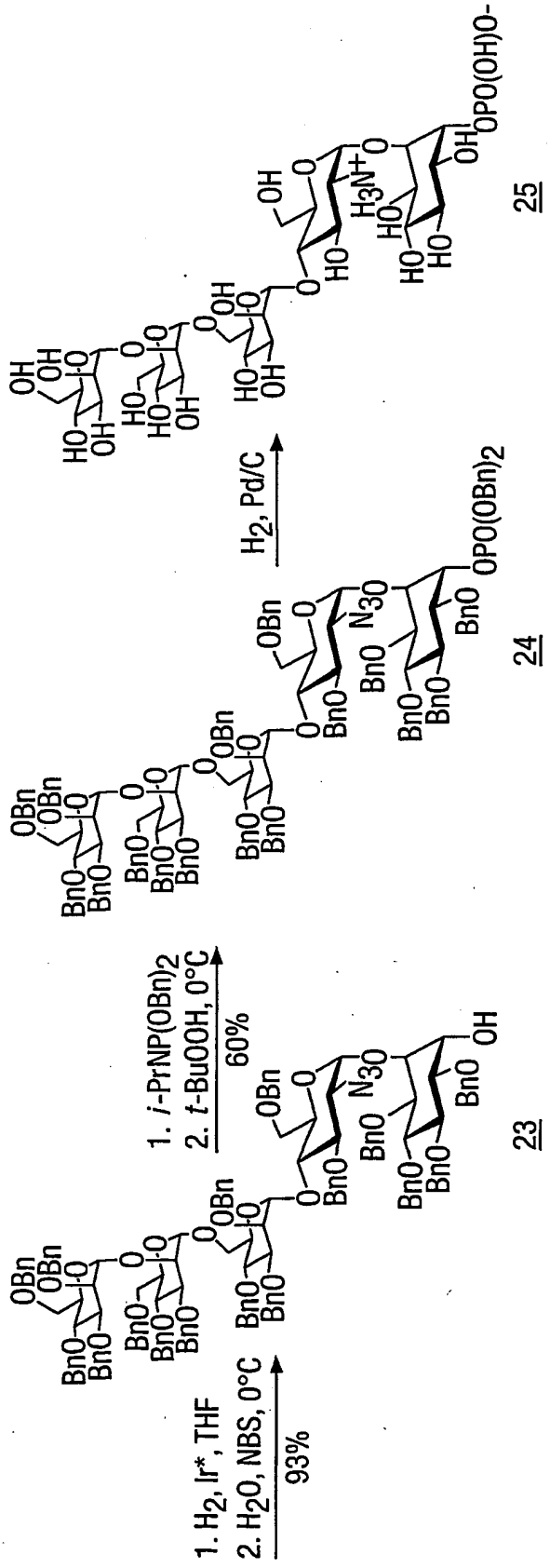

Scheme 3
NaH, BnBr
91%
1. H2, Ir*, THF
2. H2O, NBS, 0°C
84%
1. i-Pr2NP(OBn)2
2. t-BuOOH, 0°C
97%
H2, Pd/C, 10%, NaOAc/AcOH
88%
7
10
11
12
13
RGL1022

Scheme 4

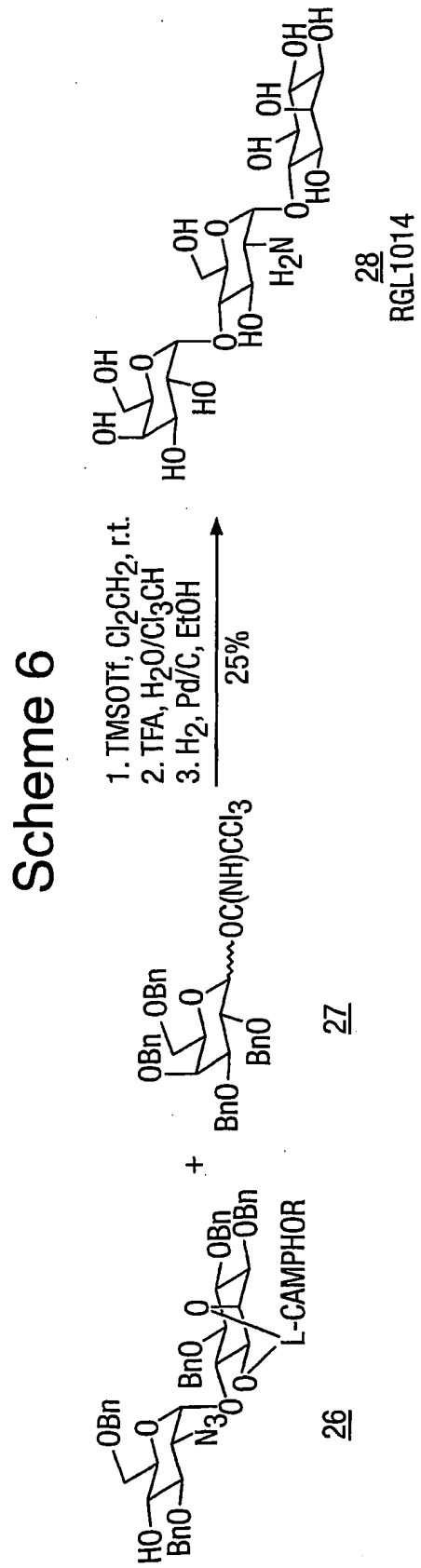

14
4
TMSOTf, Et2O, rt
70%
15
1. NaOMe/MeOH
2. NaH, BnBr
86%
16
1. H2, Ir*, THF
2. H2O, NBS, 0°C
83%
17
1. i-Pr2NP(OBn)2
2. t-BuOOH, 0°C
39%
18
H2, Pd/C, 10%,
NaOAc/AcOH
99%
19


Scheme 5 (I)
TMSOTf, CH_2Cl_2, rt
58%
1. NaOMe/MeOH
2. NaH, BnBr, DMF.
99%
20
4
21
22

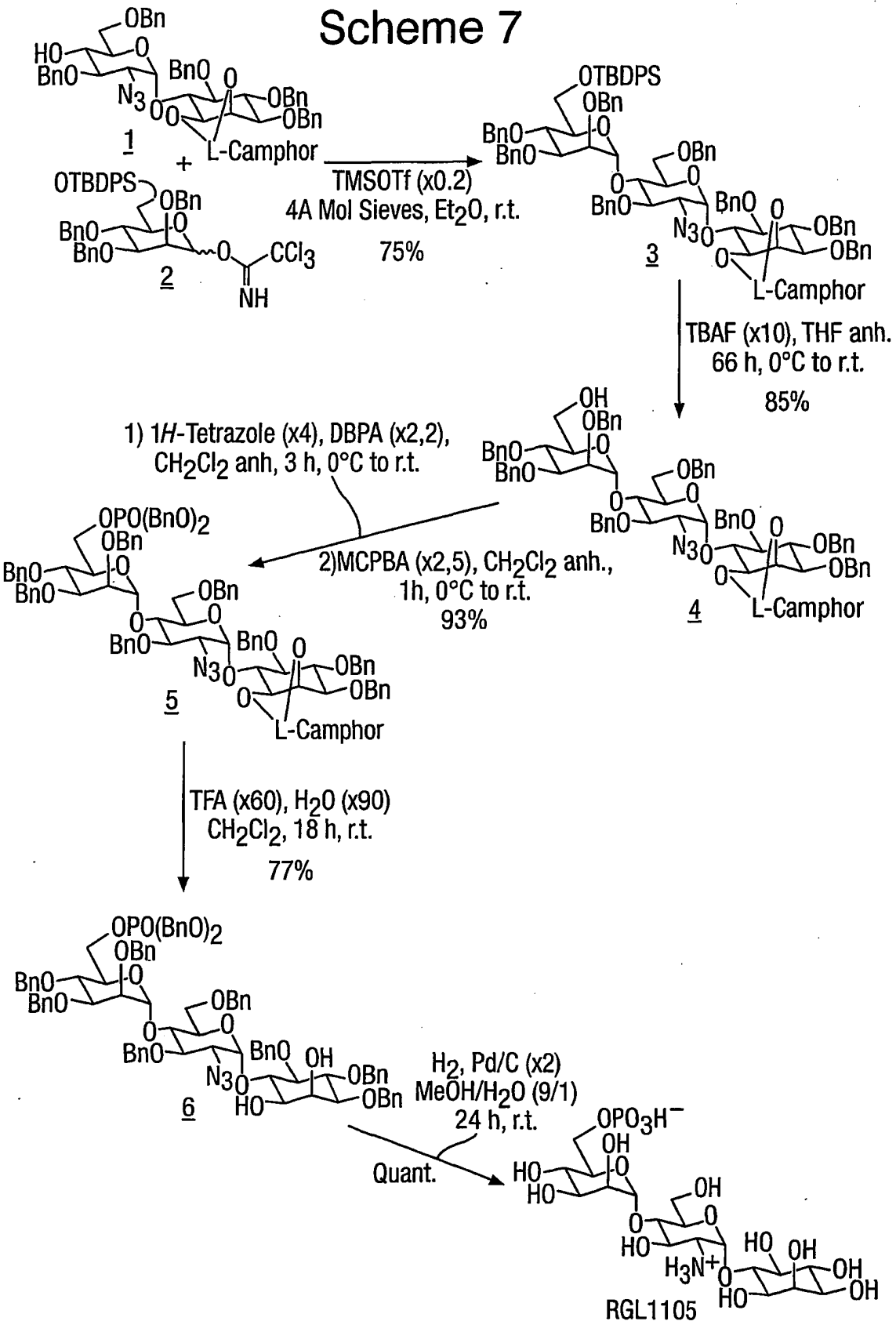
Scheme 5 (II)


1. H2, Ir*, THF
2. H2O, NBS, 0°C
93%
1. i-PrNP(OBn)2
2. t-BuOOH, 0°C
60%
H2, Pd/C
23
24
25

Scheme 6


1. TMSOTf, Cl_2CH_2, r.t.
2. TFA, H_2O/Cl_3CH
3. H_2, Pd/C, EtOH
25%
L-CAMPHOR
26
27
28
RGL1014

Scheme 7


1
2
+
L-Camphor
TMSOTf (x0.2)
4A Mol Sieves, Et2O, r.t.
75%
3
TBAF (x10), THF anh.
66 h, 0°C to r.t.
85%
4
1) 1H-Tetrazole (x4), DBPA (x2,2),
CH2Cl2 anh, 3 h, 0°C to r.t.
2)MCPBA (x2,5), CH2Cl2 anh.,
1h, 0°C to r.t.
93%
5
TFA (x60), H2O (x90)
CH2Cl2, 18 h, r.t.
77%
6
H2, Pd/C (x2)
MeOH/H2O (9/1)
24 h, r.t.
Quant.
RGL1105

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 01/02098

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H3/04 C07H15/207 C07H3/06 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP 0 845 475 A (HOECHST AG) 3 June 1998 (1998-06-03) the whole document	1-15
X,Y	PATENT ABSTRACTS OF JAPAN vol. 1995, no. 01, 28 February 1995 (1995-02-28) & JP 06 293790 A (KYOWA HAKKO KOGYO CO LTD), 21 October 1994 (1994-10-21) abstract	1-15
X	WO 98 50049 A (CORNELL RES FOUNDATION INC) 12 November 1998 (1998-11-12) claim 7	1-15

-/—

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2001	12/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bardili, W

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 375 (C-0973), 12 August 1992 (1992-08-12) & JP 04 120089 A (RIKAGAKU KENKYUSHO;OTHERS: 01), 21 April 1992 (1992-04-21) abstract	1-15
X	PATENT ABSTRACTS OF JAPAN vol. 016, no. 020 (C-0902), 20 January 1992 (1992-01-20) & JP 03 237101 A (RIKAGAKU KENKYUSHO;OTHERS: 01), 23 October 1991 (1991-10-23) abstract	1-15
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 479 (C-552), 14 December 1988 (1988-12-14) & JP 63 196596 A (KURITA WATER IND LTD;OTHERS: 01), 15 August 1988 (1988-08-15) abstract	1-12,14
X	WO 00 15254 A (INST MEDICAL W & E HALL ;SCHOFIELD LOUIS (AU)) 23 March 2000 (2000-03-23) page 5	1-12,14
Y	WO 98 10791 A (RADEMACHER THOMAS WILLIAM ;MCLEAN PATRICIA (GB); HOEFT RADEMACHER) 19 March 1998 (1998-03-19) cited in the application the whole document	1-15
Y	WO 99 38516 A (MARTIN LOMAS MANUEL ;NIETO ISABEL VARELA (ES); ALVAREZ YOLANDA LEO) 5 August 1999 (1999-08-05) cited in the application the whole document	1-15
X,Y	MÜLLER, G. ET AL.: "Structure-activity relationship of synthetic phosphoinositolglycans mimicking metabolic insulin action" BIOCHEMISTRY, vol. 37, no. 38, 1998, pages 13421-13436, XP002135715 the whole document -/--	1-15

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	JAWOREK C H ET AL: "Synthesis of an Inositol-Containing Trisaccharide Related to Insulin Signal Transduction" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 40, no. 4, 22 January 1999 (1999-01-22), pages 667-670, XP004151413 ISSN: 0040-4039 see compound 1	1-15
X	DEEG, M.A. ET AL.: "Inositol glycan phosphate derived from human erythrocyte acetylcholinesterase glycolipid anchor and inositol cyclic 1,2-phosphate antagonize glucagon activation of glycogen phosphorylase" DIABETES, vol. 42, no. 9, 1993, pages 1318-23, XP001018200 page 1319	1-15
X	FERGUSON, A.J. ET AL: "Molecular species analysis and quantification of the glycosylphosphatidylinositol intermediate glycolipid C from Trypanosoma brucei" MOL. BIOCHEM. PARASITOL., vol. 77, no. 2, 1996, pages 137-45, XP001017844 page 144	1-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10; 12-15

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the above-indicated claims is impossible. Consequently, the search has been restricted to inositol phosphoglycans as claimed in claim 11 and the corresponding subject-matter of claims 12-15.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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